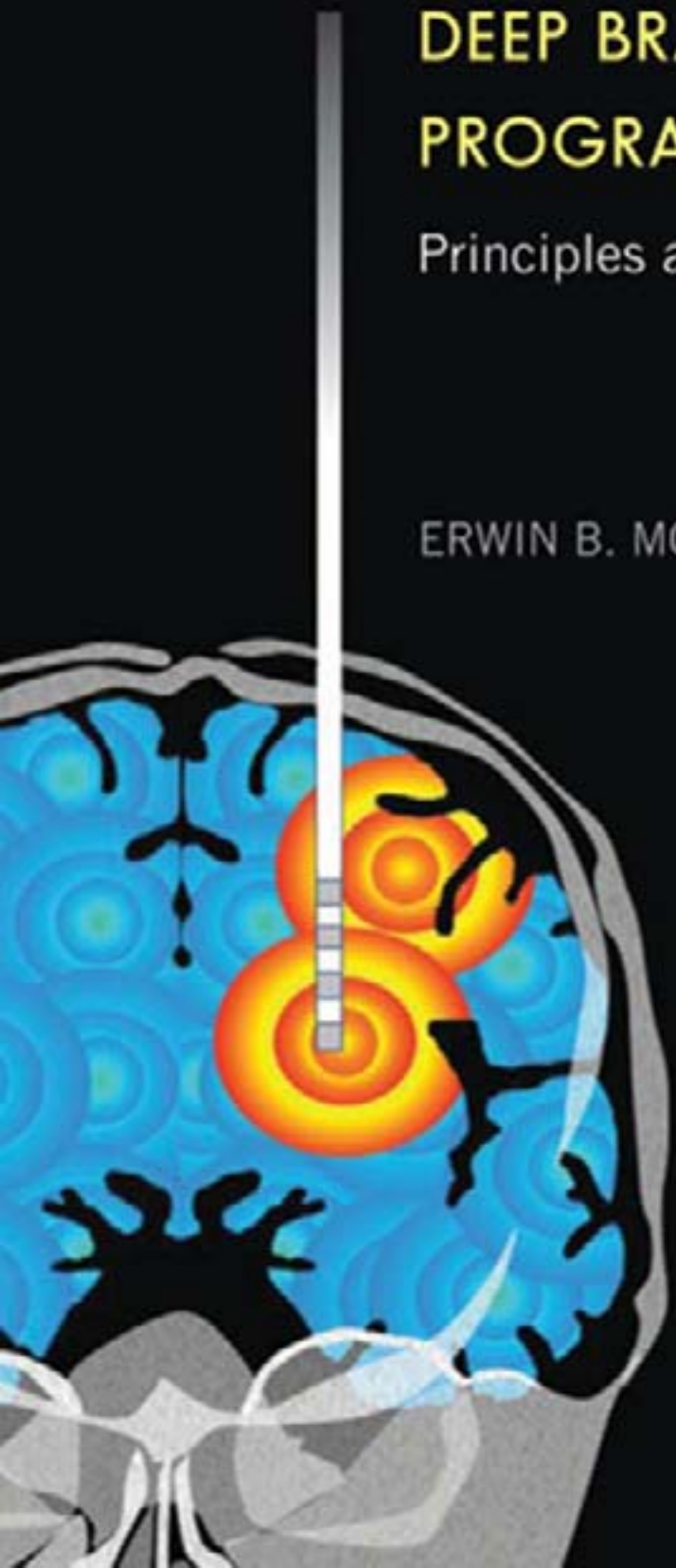
DEEP BRAIN STIMULATION PROGRAMMING

Principles and Practice

ERWIN B. MONTGOMERY, JR.



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Disclaimer

The information in this monograph on deep brain stimulation (DBS) is advisory only and is not meant to direct the specific management of any individual patient. Physicians and other health care providers must use their own professional judgment when evaluating this information and must consider the unique circumstances of each patient when providing therapy. Patients and their caregivers are strongly advised not to change patient care without approval from the treating physician or health care professional.

The field of DBS is continually evolving, and physicians and other health care providers are strongly advised to keep abreast of developments that could alter the information and advisories contained here. They should review the appropriate operation and safety manuals from the manufacturers of the equipment they use. When in doubt, they should consult the manufacturer directly.

As of this writing, the Food and Drug Administration (FDA) has approved four DBS systems from a single manufacturer. These systems differ primarily in their implanted pulse generators (IPGs). These include a single-channel IPG (Soletra; Medtronic Inc.), a dual-channel IPG (Kinetra; Medtronic, Inc.), a dual-channel IPG (Activa PC; Medtronic, Inc.), and a dual-channel rechargeable IPG (Activa RC; Medtronic, Inc.). The latter two devices became available just at this book was submitted to the publisher and before the author was able to gain extensive experience with the uses of these devices. Comments regarding these devices were based on materials made available by the manufacturer. However, the basic concepts underlying their utilization have not changed from those presented in this book.

The latter two IPGs incorporate both constant-*voltage* and constant-*current* modes of stimulation, the implications of which are discussed in the monograph. However, alternative systems are in clinical trials, and others are anticipated. Because these anticipated systems are not yet FDA approved, the details of their use cannot be discussed at a therapeutic level. Although the information provided in this monograph will help the physician in deciding which specific DBS systems to use, the decision in each case must be based on the treatment team's own assessment of the relative advantages and disadvantages of each system and the unique circumstance of the team's practice and particular patient.

This book should not be construed as an endorsement, either explicitly or implicitly, of any particular medical device or treatment. Information that may not conform to FDA guidelines is explicitly noted in the text.

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To Lyn Turkstra, a true miracle in my life, and to my sons Erwin, Steven, and Matthew, who have been constant sources of pride and joy.

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Preface

Deep brain stimulation (DBS) is a remarkable therapy. For many neurological and psychiatric disorders, DBS is more effective than the best medical therapy. For other disorders, DBS may be the only therapy (see Commentary 1.1).

It is difficult to convey the impact on the patient, family members, caregivers, and health care professionals of the nearly miraculous effect of DBS on some patients. Patients severely disabled for years are suddenly able to function nearly normally. The only comparable experience might be that which followed the introduction of levodopa for Parkinson's disease. But unlike the effects of levodopa, for some patients, the improvement with DBS is present at the click of a switch. For neurologists, the nearly immediate improvement of many neurological disorders provides a gratification not usually afforded in the discipline.

The adoption of DBS by neurologists lags far behind its promise. Several factors may explain this lag, including vicissitudes in financial reimbursement, but a potentially critical factor is that DBS appears foreign to many people in the field. Most health care professionals have never been exposed to the technology and so do not fully appreciate it. Most medical and professional schools no longer teach, or at least do not teach to an appropriate degree, the neuro- and electrophysiological principles that would facilitate the greater appreciation and acceptance of the technology, particularly in this era of molecular neurobiology. One purpose of this book is to redress this dearth of understanding of electrophysiological principles.

The lack of understanding of neuro- and electrophysiological principles makes it difficult for the physician or health care professional to feel comfortable using DBS. Often, the lack of familiarity creates the impression that DBS is "magical." In such cases, the investment in time, effort, and resources needed to learn DBS programming appears to be too great to justify, particularly when health care professionals are already overworked. Lack of knowledge and skills often results in programmers resorting to the "average" stimulation configurations and parameters and rarely venturing beyond, thereby potentially denying patients the benefit that unusual or atypical settings might provide. This is an increasing danger because some devices may offer "cookbook" guides to DBS programming, which potential programmers may take too literally. The result is that many health care providers are giving up too early (Moro et al., 2006). Often they resort to a reliance on medications that previously failed, leading to the DBS surgery in the first place.

Knowing the electrophysiology and the neuroanatomy near the DBS electrodes would make DBS far less foreign. DBS programming does not need to be magical or involve blindly trying every one of the thousands of different DBS parameters. The premise of this book is that treating patients with DBS can be made more efficient and effective by understanding the principles on which it is based. An understanding

of the fundamental principles will serve the programmer in good stead regardless of future technical developments. The knowledge will never become obsolete.

DBS is more than a remarkable therapy. It also provides a unique opportunity to probe brain function and dysfunction. Already, DBS-related research has made obsolete several cherished notions of physiology and pathophysiology. Also, the history of DBS provides remarkable insight into the strengths and weakness of how we conduct research and deliver clinical care. For example, in response to case reports of rare conditions responding to DBS, some physicians have called for randomized controlled clinical trials, but the statistical sample size required would exceed the number of potential cases in any reasonable time frame. Though not widely appreciated, DBS is a symptomatic therapy, not disease specific. Just as it would be unreasonable to require separate randomized clinical trials of a pain relief medication for every conceivable cause of pain, similar judgments should apply to DBS.

In surveying the clinical and scientific response to DBS, one is struck by how DBS is seen as intruding on more traditional therapies. The risks of DBS are often exaggerated and this sometimes discourages its use or further research. The excitement regarding DBS pales in comparison to that of stem cell treatment, despite the failure of fetal cell transplants and the lack of a cogent argument that dopamine replacement therapy with stem cells will fare any better. Interest in DBS also pales in comparison with that of gene therapy and despite the fact that the clinical benefits of DBS exceed those of gene therapy, at least at this early stage. Also, curiously missing from the discussions of both stem cell and gene therapy is mention of their surgical risks, which likely equal or exceed those of DBS because the risks are proportional to the number of times the brain is penetrated.

Assuming this apparent poorer risk-to-benefit ratio of dopamine stem cell and gene therapy, why then is there greater interest in them? The likely answer is that scientists and health care professionals are more predisposed to stem cell and gene therapy because these therapies more closely resemble current concepts of disease pathogenesis and the mistaken notion that treatment is synonymous with reversal of the pathogenesis. What could be more intuitive than the notion of dopamine cell replacement when Parkinson's disease is thought to be synonymous with dopamine cell loss? What could make more sense than converting the excitatory output of subthalamic nucleus neurons, which in the disease state excite an already overactive globus pallidus internal segment (GPi), to an inhibitory output to reduce the overactive GPi? The intuitive appeal notwithstanding, these notions are misleading (see Chapter 12).

Current research suggests that the therapeutic mechanisms of DBS action are not related to direct effects on dopamine neurotransmission. This clearly implies that there are nondirect dopaminergic mechanisms and, consequently, other potential therapeutic targets. It is likely that dopamine depletion sets up a cascade of effects throughout the basal ganglia–thalamic–cortical system, and these effects could be potential therapeutic targets. However, the lesson is clear. Pathogenesis of the disease is not synonymous with the pathophysiology, and it is the pathophysiology that leads to the disabilities associated with the disease. Failure to recognize that pathogenesis is not the same as pathophysiology likely will lead to failure to develop alternative and potentially better treatments. One could argue that the success of DBS is a case against the claims made previously. That would be the case if the development of DBS were the result of deliberate application of reason and science. The truth of

the matter is that the origins of DBS were serendipitous. DBS followed from the demonstration of therapeutic electrical stimulation effects only as a test of location preceding surgical ablation (Cooper et al., 1980).

Unfortunately, the mechanisms of action of DBS are largely unknown. However, this knowledge is increasing (Montgomery and Gale, 2008). For example, DBS at any frequency excites various neuronal elements, such as axons and presynaptic terminals in the vicinity of the DBS electrode including those that project to and from neurons in the stimulated target. In addition to generating action potentials that run down the axon to presynaptic terminals in the usually (orthodromic) direction, these action potentials travel upwards to the cell body in reverse (antidromic) direction from the usual. DBS activates axons near the stimulated target, and activation of these axons may have more to do with the therapeutic benefit of DBS than stimulation of neurons within the stimulated target. Unfortunately, none of these neuronal responses map conveniently onto preconceived notions of pathophysiology and, consequently, seem to be given little credence. It is human nature to discount observations that are counter to current theories (Johnson-Laird, 2006), but these new observations are the source of new and better theories. DBS-related research could revolutionize theories of brain function if given a chance. So far, the chances do not look good, but like Pascal's Wager, one tries to be optimistic.

The use of DBS also challenges how new therapies are justified and approved. As is the case with other complex, expensive, and less commonly used technologies, DBS has not fared well under the current preoccupation with evidence-based medicine, where randomized, placebo and blinded trials are the preferred and often the exclusive form of evidence (Montgomery and Turkstra, 2003). Case reports of DBS for rare disorders have been greeted by demands for randomized clinical trials requiring sample sizes that may exceed the numbers of candidate patients. Whereas in the past, these patients might still benefit by the "off-label" use of Food and Drug Administration (FDA)-approved devices, such off-label use is under increasing attack. Compounding the problem, the costs of such studies and the low likelihood of finding financial sponsors mean that off-label uses are not likely to become "on-label" uses and patients with off-label disorders clearly responding to DBS will not treated. The increasing FDA censorship of physicians who speak of their own judgment in recommending the long-respected off-label use of FDA-approved therapies increasingly may endanger these patients.

The importance of DBS for understanding brain function cannot be overstated. In this era of remarkable advances in molecular neurobiology, we forget that the brain is essentially an electrical device. Although the prevailing view is that neurological disease is caused by a deficiency or surplus of neurotransmitters, DBS reminds us that the brain processes information electrically. Thus, neurological and psychiatric disorders can be seen as "misinformation" related to the patterns of electrical activities in and among neurons. The old saws of clinical neurology that there are "positive" symptoms, such as abnormal gain of function, "negative" symptoms, such as loss of function, and "disconnection" symptoms need to be updated based on symptoms related to misinformation. The information and misinformation in the brain most likely is primary and proximately represented in the electrical activities of neural systems. Neurotransmitters are the messangers not the message and it is the

message that is of paramount importance.The brain has more in common with a computer circuit board than with a stew of chemicals.

The history of DBS also reflects much about the good and bad of research and clinical care. Personal accounts related to DBS have been both inspiring and disheartening. They include accounts of scientist–physicians who have displayed great perseverance and courage, such as Dr. Nicholas Schiff and his colleagues in New York in their work with DBS and minimally conscious patients, as well as physicians who have shamelessly exploited DBS for personal gain and compromised the scientific and clinical contributions that could have been made. But these accounts are for another time and place.

The primary goal of this book is to provide an aid to the many health care professionals who have volunteered to care for patients receiving DBS therapies but at the same time to enlarge the scope of the discussion as befits a truly revolutionary approach to the understanding and treatment of neurological disorders. Some will disagree with the approaches and recommendations made here. That is fine; we learn more when we disagree. However, it is important to recognize what is the basis of disagreement and the problem is that many times it appears to be based on habits and uncritical imitations of others. These do not represent knowledge. Even that is important to recognize and discuss. We should not be shy or coy about it.

Writing this book made clear the recognition of how lucky I have been. My experiences range from the outpatient clinic to the operating room, the human and nonhuman primate laboratory, and computational modeling and simulations. This led me to value the unique opportunities for cross-fertilization of ideas, particularly through interactions with colleagues representing these different areas. There is no question that insight gained in the clinic and operating room greatly facilitated work in the human, nonhuman primate, and computer laboratories. Similarly, the insights gained in the labs enhanced my abilities as a physician. This experience reinforced my belief in the unique and valued position of an academic neurologist/scientist fully immersed in the ethos of a true university. Unfortunately, such neurologists/scientists are increasingly an endangered species. The habitat for neurologists/scientists is shrinking, and it is a pity that some universities do not recognize or cynically deny the potential for the unique contributions possible by academic neurologists/scientists, perhaps as an excuse for their failure to support neurologists/scientists.

It is not possible here to recognize the many scientists whose work has greatly influenced DBS. Most of the citations in this book are to reviews or perspective papers, and I hope that interested readers will refer to those papers for citations of much of the original work.

The writing of this book was greatly aided by numerous discussions with esteemed colleagues and friends. I acknowledge discussions with John Gale, PhD, who started as an employee, became a student, then a colleague, and was always a friend. I also acknowledge a great debt to Cameron McIntyre, PhD; Jerrold Vitek, MD, PhD; He Huang, MS; Frank Moss, PhD; and the National Primate Research Center of the University of Madison–Wisconsin, directed by Joseph Kemnitz, PhD.

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Abbreviations

DBS: deep brain stimulation
GPe: globus pallidus external segment
GPi: globus pallidus internal segment
Hz: Hertz, a measure of frequency; here, of electrical waveforms
IPG: implanted pulse generator
INS: implanted neurostimulator
pps: (electrical) pulses per second
PPN: pedunculopontine nucleus
SNc: substantia nigra pars compacta
SNr: substantia nigra pars reticulata
STN: subthalamic nucleus
Vim: ventrointermediate thalamus
VL: ventrolateral thalamus (thalamic)

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Deep Brain Stimulation Programming: Principles and Practice

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I Introduction

Since the first description of deep brain stimulation (DBS) as we know it, by Cooper in 1980, DBS has rapidly expanded, both in the number of patients treated and in the range of approved indications (Cooper et al., 1980). Patients with marked disabilities who have experienced no relief from any alternatives often have remarkable improvements with DBS (see Commentary 1.1).

As will be demonstrated, the brain is basically an electronic device. Information is encoded, processed, and transmitted electronically. The neurotransmitters, which are the basis for most pharmacology, are just the messengers between neurons; they are not the message. Any information encoded in the pulsatile release of the neurotransmitters is determined by the sequence of electronic action potentials that are transmitted to the synaptic terminal. Consequently, it only makes sense that DBS should be effective and that the future for DBS and other electrophysiologically based therapies is bright (see Commentary 1.2).

For most patients, implanted DBS pulse generators (IPGs) are reasonably easy to program, but programming for others can be a challenge. There are literally thousands of possible combinations of stimulator parameters. Fortunately, most patients respond to a similar and narrow range of combinations. For others however, dedicated effort is required to identify the optimal combination. The greatest danger is that you will give up too soon. The premise of this book is that postoperative DBS programming can be made more effective and efficient by knowing some basic electrophysiological principles and some details of neuroanatomy.

In this book, I first explain the principles of electrophysiology and the details of regional anatomy and show how this information can guide effective and efficient DBS programming. Often, you can visualize in your mind the orientation of the DBS contacts to the patient's unique regional anatomy on the basis of the patient's responses to test stimulations. You can also visualize the electrical fields generated by the DBS. Matching these visualized electrical fields to the regional anatomy can quickly suggest the DBS options most and least likely to be effective.

Some programmers are adept at visualization; others are not. Some programmers find it easier to follow a specific step-by-step algorithm, so the second part of this book provides such algorithms based on anatomical and electrophysiological principles. Following these algorithms provides some assurance that you have tried the most reasonable combinations of stimulation parameters.

Two major approaches underlie the programming methods described in this book. The first is how to affect the intensity of the electrical fields, thereby exciting different neural elements in the field. This approach is accomplished by exploiting the electrophysiological principles that underlie the effects of pulse width, electrical current or voltage, and the configuration of active

Commentary 1.1. ***The Case for Deep Brain Stimulation***

Arguably, DBS is the most effective treatment for many movement disorders. It succeeds in cases when all manner of pharmacological and biological treatments (e.g., fetal cell transplants) have not. For example, in clinical trials of Parkinson's disease, all reasonable pharmacotherapies have to be unsuccessful before patients can receive DBS (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001), and despite previous treatment failures, the large majority of patients who receive DBS improves substantially. In other clinical trials, in which patients with Parkinson's disease were randomly assigned to medical therapy or to DBS, DBS produced greater clinical benefit (Schupbach et al., 2007; Weaver et al., 2009). In clinical trials of fetal cell transplants, patients regressed to baseline disability within 12 months (Olanow et al., 2003), whereas those receiving DBS experienced sustained benefit for 5 or more years (Krack et al., 2003; Pahwa et al., 2006). Indeed, the majority of patients who received fetal cell transplants experienced "runaway" dyskinesias that were controlled in many cases with DBS (Graff-Radford et al., 2006; Olanow et al., 2003). To date, no one has argued convincingly that stem cell implantation will be any better than fetal dopamine cell transplantation. Although gene therapy is still in early development, studies in which glutamic acid decarboxylase is transfected into the subthalamic nucleus report benefits on the order of 30% (as measured on the Unified Parkinson's Disease Rating Scale) (Kaplitt et al., 2007). In contrast, DBS provides sustained improvement on the order of 50% or higher. The benefits of intraparenchymal injections of nerve growth factors in patients with Parkinson's disease have been no better than those with placebo. The potential risks of stem cells transplants, viral vector-mediated gene therapies, and intraparenchymal injections of biological agents are not likely to be any less than those of DBS. All require surgical invasion of the brain.

Similarly, DBS is successful in other conditions in which pharmacotherapy has failed, such as essential tremor (Koller et al., 1997), tremor secondary to other causes (e.g., multiple sclerosis) (Montgomery, 2008a), pharmacologically refractory depression (Mayberg et al., 2005), obsessive–compulsive disorder (Abelson et al., 2005), and the hyperkinetic symptoms of Tourette's syndrome (Shahed et al., 2007).

Despite its clinical superiority and relatively modest risks, DBS has not captured the imagination of neurologists, geriatricians, generalist physicians, or the public at large, as has stem cell transplantation or gene therapy. This lack of attention is important and intriguing, and it has implications for the nature of scientific progress in general. Perhaps pharmacological, stem cell, and gene therapies provide the comfort of familiarity. Perhaps these therapies are seen as natural extensions of current theories of disease pathogenesis and pathophysiology. If these reasons are true, it is a false comfort because many of the current theories of physiology and pathophysiology are fatally flawed (Montgomery, 2007a), and continued adherence to them will only delay new knowledge and better treatments. Perhaps it is because medical schools now

teach less physiology, particularly systems physiology, and relatively more molecular biology and pharmacology. Even most current theories of basal ganglia physiology and pathophysiology are not physiological in nature. Rather, they are inferences from anatomy and pharmacology: they are based on the paradigms of *anatomy as physiology* and *pharmacology as physiology* (Montgomery, 2007a). Abraham Maslow's adage, "When the only tool you have is a hammer, everything looks like a nail," is relevant here; many neurological disorders are still thought to be neurotransmitter disorders, and Parkinson's disease is thought to result from dopamine deficiency.

Deep brain stimulation has a great deal to teach us, if we will but listen. Already, it is clear that the mechanisms of DBS are not analogous to those of pharmacotherapy. DBS is telling us something radically new and different.

Commentary 1.2 ***The Future of Deep Brain Stimulation***

Many people comment on the remarkable success of DBS (see Commentary 1.1). However, the real question is, why are they so surprised at this success? The brain is basically an electrical device. Information is processed by integrating excitatory and inhibitory postsynaptic *electrical* potentials, and information is encoded in the subsequent train of *electrical* action potentials. Neurotransmitters, released at the synaptic junctions, are just the messengers; they are not the message. One merely has to consider the timescale of operations to understand the difference between electrical and pharmacological effects. DBS operates on the order of milliseconds. For example, the time difference between effective DBS at 130 pps and ineffective DBS at 100 pps is 2.3 ms, which is the difference in the interstimulus pulse intervals. Yet this small difference of 2.3 ms is sufficient to cause a difference in efficacy, with 130 pps DBS being effective and 100 pps not. Pharmaceutical agents operate over minutes to hours and cannot replicate the precise timing of information in the brain.

It is the message in the brain that is abnormal, save for the most peripheral motor and sensory functions of the brain, and it is this misinformation that causes the symptoms and signs of disease (see Chapter 11) (Montgomery, 2004a). Because the message is fundamentally electric, the message should be manageable electrically (see Chapter 3).

Theoretically, several electrophysiological approaches could be applied to treat misinformation, depending on the nature of the misinformation. One type of misinformation may be a low signal-to-noise ratio. In this case, the actual information is present but buried in noise. The signal-to-noise ratio can be improved, along with symptoms and signs, by resonance amplification using DBS. There may also be two types of resonance amplification. The first depends on a specific frequency and on a regular or constant interstimulus DBS interval. Resonance then depends on the frequency of DBS relative to the fundamental carrier frequency of the neural oscillators involved (see Chapters 12 and 14).

(*continued*)

Commentary 1.2 (*continued*)

A second type of resonance amplification is stochastic resonance, which is the counterintuitive notion of adding noise to a signal to improve the signal-to-noise ratio (Hanggi, 2002). Although the noise added to the signal has to be a certain bandwidth (the range of frequencies contained in the noise), the advantage of stochastic resonance is that the fundamental frequencies of the underlying neural oscillators do not have to be known precisely. Stochastic resonance has been implicated in improved speech perception in patients undergoing cochlear implants (Chatterjee and Robert, 2001; Zeng et al., 2000) and in balance control (Priplata et al., 2002).

Another approach to correcting misinformation is to overwrite the misinformation with no information. Overwriting can be accomplished by stimulating and driving the neurons to fire in a highly regular manner so as to strip the neuronal spike trains of any information (Grill et al., 2004; Montgomery and Baker, 2000).

Other novel approaches to correcting misinformation include attempts to replicate the normal patterns of neuronal spike trains, although this replication is a major challenge. Another approach consists of closed-loop DBS, in which sensors in the brain detect specific brain states and then trigger a brief train of DBS.

Another major challenge for DBS is to identify new targets for an expanding number of neurological and psychiatric disorders. In the past, DBS targets were identified by targeting those structures historically surgically ablated, an approach called "chasing lesions." If this approach were to remain the only means of identifying DBS targets, the future would be very limited indeed. Fortunately, other methods for defining DBS targets have been tried. For example, positron emission tomographic scans of patients with medically refractory depression reveal areas of increased and decreased metabolism.The subgenu cingulum with increased metabolic activity was selected for DBS. Although this choice was based on what is now an outdated notion of how DBS works (that inhibiting the stimulated target is the goal of therapy), preliminary studies suggest that the subgenu cingulum may be an effective DBS target for treating depression (Mayberg et al., 2005).

Perhaps the most common conception of how functions are represented in the brain is that the brain has modular oraganization. According to this notion, specific areas in the brain perform specific functions and although these functions are integrated to cause the final behaviors, the integration is piecemeal and often sequential. An alternative conception, the Systems Oscillators theory (Montgomery, 2004a, 2007a, 2008a; Montgomery and Gale, 2008), is that the brain is composed of sets of loosely coupled interconnected networks of oscillators made up of reentrant activity in closed feedback circuits. Although specific networks or aspects of networks vary in their anatomical location, they act more as a whole and virtually simultaneously or in parallel. In the case of physiological functions, being distributed throughout the network rather than restricted to a specific structure implies that a physiological function can be

targeted by DBS anywhere within that network. The advantage of targeting a system rather than a specific structure is that other targets may be identified in the system, some of which might be better surgical candidates, given ease of approach and risks. It would be interesting to extend the Systems Oscillators theory, in which DBS affects systems and not just structures, to determine whether DBS to areas of decreased metabolism would improve depression.

Another approach to developing DBS targets is to thoroughly explore the neurophysiology. Schiff and colleagues developed such an approach in minimally conscious patients on the basis of preliminary imaging and electrophysiological studies in nonhuman primates (Schiff et al., 2007).

The potential for electrophysiological treatments of neurological and psychiatric disorders is just beginning to be appreciated. DBS and related technologies have tremendous potential, given both the spatial and the temporal specificity of the therapies. In contrast to bathing the entire brain in pharmacological therapies for extended periods, DBS has a spatial resolution measured in millimeters and a temporal resolution measured in milliseconds. DBS differs markedly from pharmacological therapies, and in those differences lie its unique advantages in treating neurological and psychiatric disorders.

electrical contacts. This first approach is generally aimed at improving the efficacy of DBS for symptomatic control.

The second approach is to affect the shape, size, and anatomical location of the electrical field by exploiting the electrophysiological principles underlying the effects of electrical current or voltage and the configuration of active electrical contacts. Varying the intensity of the electrical field generally affects efficacy, whereas varying the size, shape, and anatomical location of the electrical fields generally allows you to avoid side effects and complications. These general principles of electrical stimulation of neural elements provide a context for understanding how you can exploit electrophysiological principles for effective and efficient DBS programming.

Principles of Effective and Efficient Programming

As more patients receive DBS IPGs, the need for health care professionals who are capable of providing the postoperative management of these systems will increase. Currently, the relative lack of such trained health care professionals makes getting emergency care problematic for patients. Many physicians are reluctant to become involved in postoperative DBS management. The reasons are multiple and varied, and include but they include apprehension based on unfamiliarity. Often, the health care professional's only exposure to electrophysiology was a short, rudimentary lecture in medical school. Consequently, some health care professionals look at DBS programming as though it were "magical." Alternatively, others may believe that the complexity of DBS programming reduces the cost-effectiveness of the therapy. Neither belief is true.

Effective DBS programming is guided by biological and electrical principles. In many ways, these principles are analogous to the principles of pharmacokinetics and

pharmacodynamics that underlie rational pharmacological treatments. These pharmacological principles can be used explicitly, although more often they are used implicitly by being embedded in clinical algorithms. However, in problematic patients, explicit consideration of pharmacological principles is often necessary to provide effective treatment. The same is true for the principles of electrophysiology that underlie DBS.

Proximate Effects and Distal Interventions: What the Brain Sees versus What You See

A fundamental fact, true of both pharmacological and DBS treatments, is that the interventions used by health-care professionals are often distant or removed from the proximate mechanisms of action. This fact is particularly true in neurological and psychiatric disorders. The use of levodopa for Parkinson's disease is illustrative. Levodopa, by itself, is ineffective. Levodopa must be converted in the brain to dopamine. This conversion involves several steps, each a potential source of error or complications. Dopamine cannot be given directly because it does not pass the blood–brain barrier, whereas levodopa does. Getting into the brain requires an enzymatically mediated transport that can be blocked by large, circulating neutral amino acids resulting from a large protein meal.

Furthermore, before levodopa can get into the brain, it must get into the blood from the gastrointestinal tract. Even here, the problems are numerous, such as a restricted region of the small intestine for absorption and the requirement of an enzymatically mediated transport mechanism. The dopamine derived from levodopa not only acts in the striatum to counteract the motor symptoms and signs but also acts elsewhere, producing side effects.

These difficulties with levodopa are not surprising or novel to the health care professional. Indeed, these vagaries of levodopa treatment are explicitly or implicitly recognized in treatment algorithms, and most health care professionals are comfortable prescribing levodopa compounds. But what if there were no knowledge of the pharmacokinetics and pharmacodynamics of levodopa? The same variability in the clinical response of individual patients would be encountered with or without this knowledge. However, without this knowledge, levodopa management would seem magical. Treatment algorithms would be trial-and-error, and not even "educated" trial-and-error. The associated uncertainty is manageable because levodopa treatment has relatively few options. Imagine if there were thousands of formulations of levodopa, corresponding to the thousands of possible electrodes, voltages, pulse widths, and stimulation frequencies available with DBS. What makes DBS management feasible is the electrophysiological principles that reduce the range of uncertainties.

The key to effective postoperative DBS management is to develop approaches or algorithms that map DBS treatment options to the therapeutic effects of stimulation at the local neural level. We manipulate the electronics to change the electrophysiology of neuronal activities.

The Basis of DBS Effects

Although the precise mechanism of therapeutic action of DBS is unknown, it is increasingly clear that it depends on the electrical excitation of neural elements and

not on suppression (Montgomery and Gale, 2008). Most evidence suggests that DBS effects rely on the electrical excitation of axons because they have the lowest threshold to stimulation. How stimulating axons improves neurological and psychiatric disorders is unclear. Indeed, research into the mechanisms of DBS has revealed more about how the brain works than about how DBS works. DBS has already proven that current notions of pathophysiology, particularly of disorders of the basal ganglia, are simply wrong (Montgomery, 2007a) (see Chapter 12).

The key to successful DBS is to excite the intended neural elements while preventing the unintended excitation of other elements. As discussed later, stimulating the neural elements effectively depends on changing the distribution of electrical charges on the cell membrane. The control of electrical charges is determined by the principles of electronics; consequently, an explanation of these principles is in order.

Electricity is the flow of electrons through a conductor. The flow is powered by an *electromotive force* or *voltage*, measured in volts (V). The number of electrons passing a given point in a given time is the *current*, measured in amperes (A). The total amount of electrical charge delivered is measured in coulombs. The flow of electrons is also opposed by *resistance* or *impedance*, measured in ohms. The relationship among these concepts is described by Ohm's law:

$$I = E/R \tag{1.1}$$

where I is current, measured in amperes; E is electromotive force, measured in volts; and R is resistance or impedance, measured in ohms. Greater resistance requires more volts to deliver the same current.

Resistance and impedances are similar concepts, but they are not synonymous. Both concepts refer to the resistance to the flow of electrical charges, which in the case of most electrical devices is the flow of electrons through a conductor. Resistance refers to the opposition to the flow of electrical charges in response to a constant voltage. However, when the voltage fluctuates, the opposition to the flow of electrical charges will vary. This opposition to the flow of electrical charges with varying voltages is termed impedance. Thus, a conductor will offer different opposition to the flow of electrical charges when the voltage is constant or fluctuating. Furthermore, the impedance of the same conductor will vary depending on how fast the voltage is changing.

DBS systems use pulses of electrical energy; consequently, both the voltage and the current will vary over time. For this reason, the impedance is a better measure of the opposition to the flow of electrons than is resistance. IPGs differ on whether voltage or electrical current is controlled. In constant-*voltage* IPGs, the maximum voltage associated with each pulse is controlled but the maximum current will vary depending on changes in the impedance (and capacitance, explained later, see Figure 2.4). Thus, constant-*voltage* IPGs introduce another variable that must be accounted for during DBS programming—impedance. Constant-*current* IPGs control the maximum electrical current and will automatically adjust the voltage depending on the impedance (and capacitance).

Constant-*current* IPGs provide a specified amperage (electrical current), whereas constant-*voltage* IPGs provide a specified voltage, not electrical current. The amount of electrical current delivered with a constant voltage depends on the impedance

(resistance) to the flow of electrical current. Even if the stimulation voltage is kept constant, doubling the impedance (resistance) will approximately halve the current delivered to the brain. The voltage parameter on the constant-*voltage* IPG does not indicate how much electrical current is being given; you must know the resistance to determine this critical component of the DBS effect. Note that the terms "constant-*current*" and "constant-*voltage*" do not mean that there is the same electrical current or voltage at all times. Rather, DBS applies pulses of electrical stimulation, typically a "square wave" in which the voltage or current increases (or decreases) from zero to some maximum value that is maintained for a period of time and then returns to zero. The maximum and minimum amplitude of each pulse is constant in either electrical current or voltage depending on the type of IPG.

The primary factor effecting neural activation is the charge density, which is the amount of electrical charge, measured in coulombs, per unit time and surface area. Thus, other means of controlling activation of neural elements include the surface area of the electrical contacts and the width of the stimulation pulse (referred to as pulse width in DBS programming).

Because constant-*voltage* IPGs and constant-*current* IPGs are available and more are anticipated, I use the term *current/voltage* to describe the strength or amplitude of the DBS pulse that applies to the IPGs. When explicitly referring to a constant-*current* IPG, the reader should read "current/voltage" as "current," and if referring to a constant-*voltage* IPG, it should be read as "voltage." However, remember that "current" and "voltage" are not synonymous. For example, applying the same current to different electrical contacts will produce the same flow of electrical charges, even if the impedance differs between the contacts. However, applying the same voltage to different contacts will not necessary result in the same electrical current if the impedances are different and therefore will not necessarily produce the same physiological or clinical effect. The analogy of constant-*voltage* DBS to pharmacological therapies would be to write a prescription for levodopa without knowing what dose the pharmacist actually provided to the patient. Such a circumstance does not mean that you cannot treat the patient, but you have to readjust the dosing each time the patient gets a new prescription. For constant-*voltage* IPGs, the dial is set in volts, but if you do not know what the resistance of the tissue is, you cannot know how much electrical charge is being delivered—a problem analogous to not knowing what the dose of levodopa is for any pill with the dose analogous to the current.

The important and not completely clarified question is, "How much does the impedance vary over time for an individual patient and between patients?" The current understanding is that early following DBS lead implantation, the impedances within the same patient can vary widely, thereby placing a constant-*voltage* IPG at a disadvantage. Some studies suggest that over the long term there is relatively little change in the impedances (Sillay and Montgomery, 2008). However, there is considerable variability in the long-term impedances between different patients. This makes comparing DBS clinical effects between patients difficult when using a constant-*voltage* IPG, thereby making it difficult to apply knowledge and experience gained from one patient to another when using the constant-*voltage* IPG. In other words, using constant-*voltage* IPGs makes it very difficult to learn from past experience with other patients and apply that knowledge to future patients.

2

Principles of DBS Electronics

The clinical effects of DBS result from depositing electrical charges in brain tissue. How the electrical charge is deposited depends on the electronics of the DBS IPGs, which is what you manipulate to deliver the electrical charge. Consequently, you need to know how controlling the electronics controls the deposition of the electrical charge into the brain.

Likening the flow of electrical charge (current) to the flow of water is helpful. Imagine the situation shown in Figure 2.1. You have to put out a fire using a hose connected to a water tank. The amount of water coming out of the hose per unit time corresponds to the *flow of electrical charge* or the *amount of charge per unit time measured in amperes.* In the case of DBS, current is usually expressed in units of milliamperes (ma). The total amount of water coming out of the hose corresponds to the total amount of electrical charge, measured in coulombs. The amount of charge in DBS typically is measured in microcoulombs (μC). The amount of water flowing from the hose depends on the diameter of the hose: the smaller the hose, the more resistance (impedance in DBS) there is to the flow of water. Think of the difference between drinking through a small soda straw and drinking through a larger one. The diameter of the water hose corresponds to the impedance of the DBS electrodes. In the brain, the electrical properties of the tissue between the negative and positive contacts determine the resistance to electrical flow in the brain.

A special type of resistance is related to fluctuating electrical currents, such as those used in DBS. For example, alternating current (AC) power sources provide a current that fluctuates like a sine wave. In some countries, the frequency of the sine wave for AC power is 60 Hz; in other countries, it may be 50 Hz. This type of resistance is called *impedance*, and it is measured in ohms (Ω); the higher the frequency of the electrical current, the higher the impedance to the same electrical current flow. DBS uses pulses of electrical energy by varying the amount of electrical current or voltage over time (although the maximum electrical current or voltage is kept constant). Consequently, impedance is the more appropriate measure of the opposition to the flow of electrical current.

You can also adjust the amount of water coming out of the hose by changing the water pressure through raising or lowering the height of the water tank. In this case, the water pressure corresponds to electromotive force or voltage, which corresponds to the force that moves the electrical charges, and it is measured in volts (V). Electrical charge flows from the negative DBS contact (also called the cathode) as an administered negative electrical charge. Electrical charge flows toward, and is returned by, the positive contact (also called the anode). Flow of negative electrical charge is termed *cathodal* current, and the return flow is called the *anodal* current. The distinction

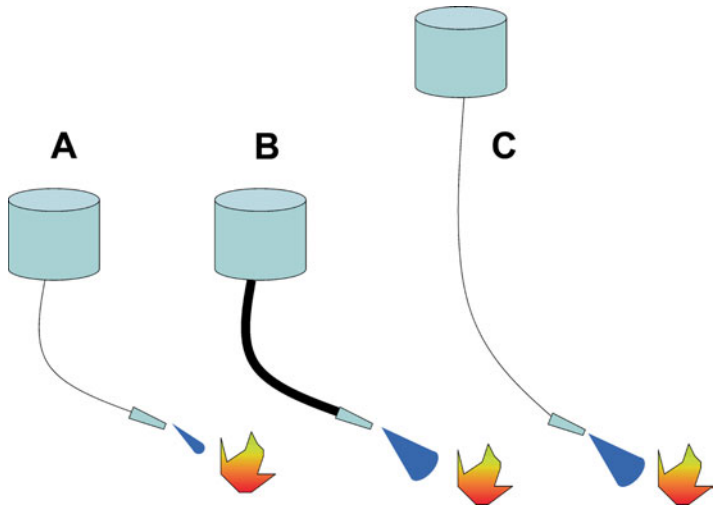

FIGURE 2.1. *The flow of water as an analogy for understanding the flow of electrical charges. The flow of electricity is controlled by the electronics. Imagine that you have to put out a fire using a hose connected to a water tank. Several factors influence how much water will flow through the hose. One factor is the diameter of the hose. A small-diameter hose (A) will have greater resistance or impedance to the flow of water and therefore will provide a lower flow of water than that from a wide-diameter hose (B). Another factor is the water pressure, which is determined by the height of the water tank. A higher tank generates greater pressure (C) and will result in a greater flow through the same diameter hose than will lower pressure (compare A and C). Similarly, a wide-diameter hose from a low tank (B) provides the same water flow as a small-diameter hose connected to a high tank (C). In electronics, higher voltage (corresponding to the water pressure created by the height of the water tank) or lower impedance (corresponding to the resistance by the diameter of the hose) can increase the amount of the electrical charge per unit time, or electrical current.*

between *cathode*, an electrical contact, and *cathodal*, the flow of negative electrical charges, should be kept in mind.

As explained in Figure 2.1, electrical current (amperage) and voltage are not the same and, thus, constant-*current* IPGs and constant-*voltage* IPGs are not the same. The same voltage (corresponding to the height of the water tank) will not produce the same water flow (current) when the impedance (the diameter of the hose) is different. Constant-*current* IPGs compensate for different impedances by automatically adjusting the voltage. The water analogy can also illustrate the difference between constant-*current* stimulation and constant-*voltage* stimulation (Figure 2.2).

Another useful analogy to understand the advantage of a constant-*current* stimulator is driving a car over a hilly road (Figure 2.3). Stepping on the gas pedal is analogous to the voltage. The speed of the car is analogous to the electrical current, which is the prime determinant of neuronal responses. The height of the hill and the effects of gravity on the car represent the impedance. If you keep the gas pedal at the same point (constant-*voltage*), the car will slow down (less electrical current and possibly loss of effectiveness) when going up the hill and speed up (more electrical current and possibly more side effects) when going down the hill. Cruise control (a constant-*current* stimulator) automatically adjusts the gas pedal (voltage) up and down on the hills (impedance) to keep the car going at the same speed (electrical current and clinical response). Furthermore, even in those patients whose impedances stabilize some period of time after DBS lead implantation, different contacts on the same DBS lead can have widely varying impedances. This makes generalization of experience using constant-*voltage* IPGs problematic because

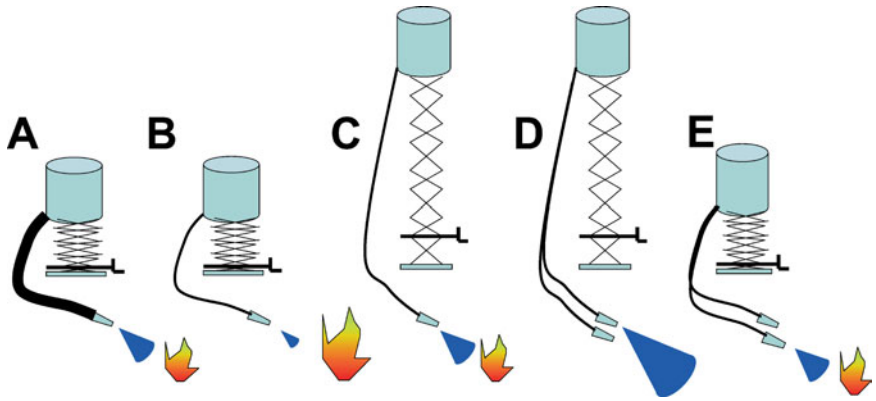

FIGURE 2.2. *Why electrical current and voltage are not the same. In constant-*current *stimulation, suppose you switch from a contact with low impedance (a wider-diameter hose; A) to a contact with higher impedance (a smaller-diameter hose; B). If you do not also increase the voltage, less electrical charge will be delivered to the brain (B). The consequence could be a loss of therapeutic effectiveness. If you switch from a single contact with high impedance (a small hose diameter) and high voltage (a high water tank; C) to two contacts, each with the same impedance (hose diameter; D), the overall impedance will drop, and more electrical current will be delivered to the brain. Excessive electrical current flow into the brain can be dangerous. Consequently, you have to lower the voltage (the height of the water tank) to give the proper amount of electrical current (E). Programmers using a constant-*current *IPG do not have to be as concerned about excessive current. The constant-*current *IPG is constantly adjusting the voltage (the height of the water tank) to ensure that the same amount of electrical charge is being delivered, regardless of the impedance of the contact or contacts.*

effects or side effects associated with stimulation of one electrode contact often cannot be applied to a different contact on the same DBS lead in the same patient because the impedances may differ.

Note Regarding Impedances

With the proliferation of IPGs, each differing in their methods for determining impedances, the programmer needs to be familiar with the nuances of each type of IPG he or she plans to use, particularly when using constant-*voltage* IPGs. Changes in voltage, pulse width, and configuration of active contacts can affect the impe-dance, which in turn affects the amount of electrical current being injected into the brain. Without careful attention to these parameters, it is possible to exceed the accepted safety limits (see Chapter 8).

Because impedances are dependent on the frequency content of the stimulation, checks of the impedances associated with different frequencies in the same system will produce different results. Note that the frequency content of the stimulation train is not just the rate at which the DBS pulses are given. The waveform of each stimulation pulse also contributes to the frequency content (see discussion of the Fourier transform in Chapter 14). For checking the electrical integrity of the DBS system electrode impedance measurements (impedances measured at specific stimulation parameters and electrode configurations that are not specifically those used in providing therapy), the specifics of the stimulation frequency content are not critical. However, for measurements of the therapeutic impedances (the impedances based on the specific stimulation trains used to provide clinical effects) which are critical to efficacy and safety, the specific electrode configurations and parameters are critical. The electrode impedances are used primarily to test the structural and electrical integrity of the DBS systems. Most electrode impedances are tested with

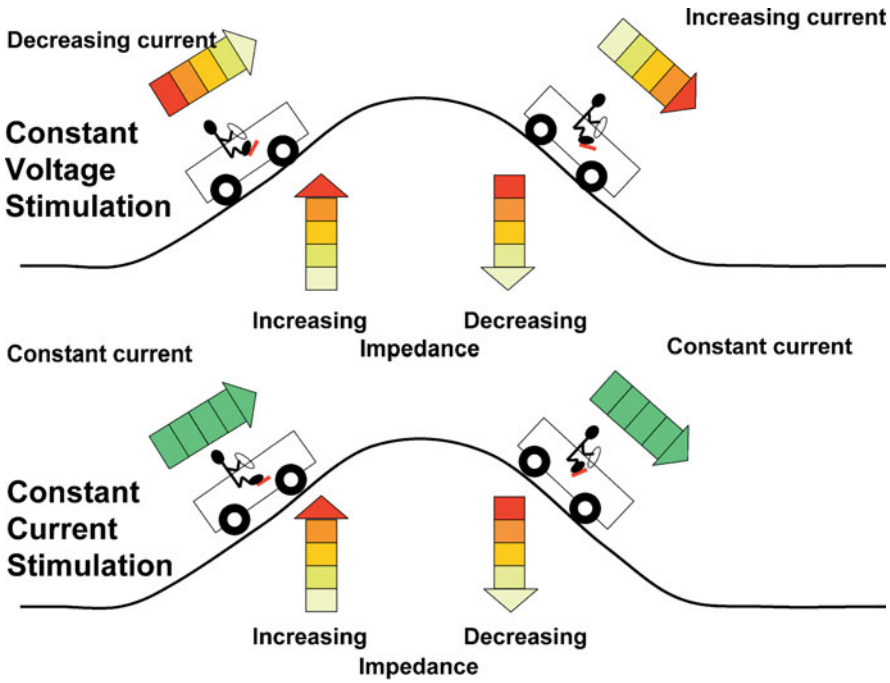

FIGURE 2.3. *Analogy of the car on the hill to electrical current delivered by DBS. The gas pedal is analogous to the voltage, the height of the hill and the effects of gravity on the car represent the impedance, and the speed of the car is analogous to electrical current (arrows). If the driver keeps the gas pedal at the same position (constant-*voltage *IPG) as the car goes up the hill (increased gravitational effects causing greater impedance to the car), the car will slow, corresponding to less electrical current. As the car goes down the hill, representing a decrease in impedance, the car speeds up, delivering more electrical current. A constant-*current *IPG is analogous to cruise control: It automatically adjusts the gas pedal to keep the car going at the same speed, whether going up or down the hill.*

manufacturers' default stimulation parameters. Some of these parameters may or may not be changed by the programmer. In some IPGs, the choice of voltage in the electrode impedance tests can affect the range of impedances that can be measured. For example, in one IPG a voltage of 0.25 V allows specific impedance measures up to 4000 Ω, 0.7 V up to 10,000 Ω, 1.5 V up to 20,000 Ω, and 3 V up to 40,000 Ω.

The dependence of impedance measures on the voltage for some constant-*voltage* IPGs presents problems when assessing therapeutic impedances. For some IPGs, the voltage used therapeutically may not be sufficient to allow an accurate measure of the impedances. This could cause confusion regarding the structural and electrical integrity of the IPG. One way to check would be to measure the electrode impedances and note any discrepancies between the electrode and therapeutic impedances. For example, a patient can have very high therapeutic impedances, typically with a low stimulation voltage, suggesting an electrical discontinuity such as a lead fracture, yet the electrode impedances are within normal operating limits. In this case, the therapeutic impedances could be checked with higher stimulation voltages. Also, the possibility of inaccurate therapeutic impedances could potentially result in the inability to ensure the safety of the DBS. If the therapeutic impedances underestimate the actual impedance, then voltages thought safe could result in

excessive electrical current being injected into the brain. If the therapeutic impedances overestimate the actual impedances, then the programmer might unnecessarily avoid higher voltages.

Many constant-*voltage* IPGs assume the impedance when assessing the safety of a particular electrode configuration and stimulation parameters. If the therapeutic impedance is significantly lower than the assumed impedance, the warning may not be issued when it should. If the therapeutic impedance is significantly higher, then a false warning may be given. Two newer IPGs have a two-tier safety warning. The first is based on assumed impedances. If the programmer continues with the planned electrode configuration and stimulation parameters, a second warning may be issued based on the measured impedances. The latter is more relevant for safe DBS. Consequently, the value of the first warning is not clear, and its incorporation into the DBS may be a legacy from prior IPGs. A problem might arise if the actual impedance is significantly higher than the assumed 500 Ω and the programmer does not elect to proceed, perhaps based on the first warning, but, rather, foregoes increases in DBS strength. Note that these problems are less likely with constant-*current* IPGs.

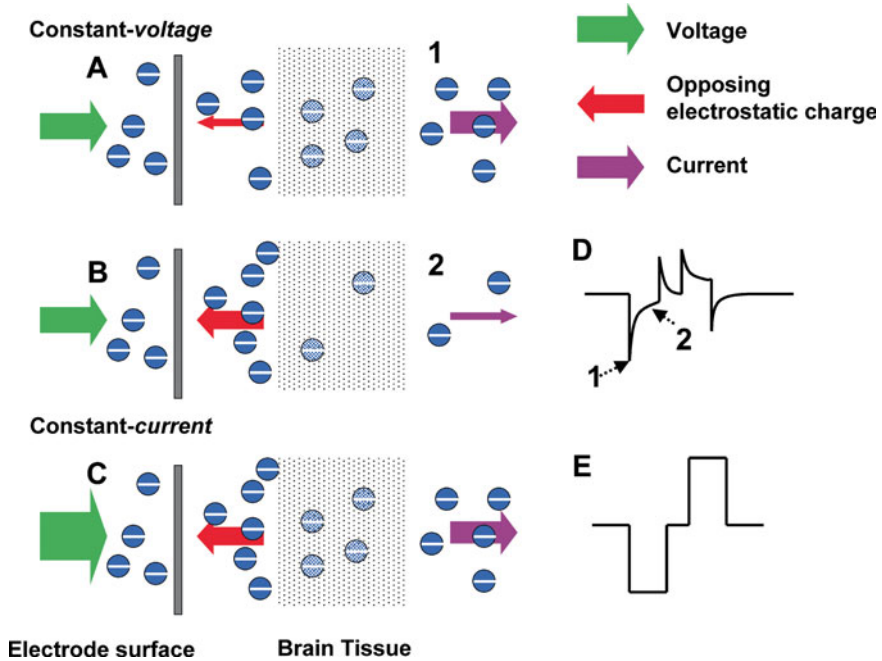

FIGURE 2.4. *Brain tissue is not a good conductor of electrical charge compared to the metal electrical contacts in the DBS lead. Consequently, as the voltage applied to the electrical contact forces electrical charge into the brain, there is a buildup of electrical charge at the electrode–brain interface (A). As the buildup increases, there is an increasing opposing electrostatic charge that counters the stimulation voltage and the result is less electrical charge flowing into the brain (B). Once the phase of stimulation is complete, the accumulated electrostatic charge acts as a battery and causes a reverse electromotive force (voltage). This is seen when the electrical voltage resulting from the DBS pulse is measured in the brain tissue (D), as seen with a constant-*voltage *IPG. The constant-*current *IPG is able to adjust the stimulation voltage to counter the buildup of electrostatic charge and thereby maintain a more constant electrical current in the brain tissue (E). (Adapted from Miocinovic et al., 2009.)*

The ability to drive electrical current into the brain is affected by impedance as described previously. However, it is also affected by capacitance. The metal conductor in the electrode contact of the DBS lead is an excellent conductor of electrical current. However, the brain tissue is not. In addition to the impedance to electrical charge coming from the electrode, there is also capacitance that causes electrical charge to collect or pile up on the interface between the electrode surface and the brain surface (Miocinovic et al., 2009) (Figure 2.4). This build of electrical charge causes a repulsive force that opposes the continued flow of electrical charge into the brain. Consequently, there is a falloff of the electrical current. When the stimulation pulse stops, the accumulated charge at the electrode–brain interface acts as a battery that sends charge back into the electrode. The result is a complicated DBS pulse waveform (see Figure 2.4) that may not be optimal for exciting neural elements.

The constant-*current* IPG adjusts for the buildup of opposing force due to capacitance by automatically increasing the voltage (see Figure 2.4). The result is a truer square-wave DBS pulse waveform that may be more optimal for stimulation, and this may be a significant advantage for constant-*current* IPGs. The constant-*voltage* IPG cannot adjust for the opposing buildup of electrostatic charge.

3 Principles of Electrophysiology

Therapeutic Mechanisms versus Delivery of Therapy

The pharmacological treatment of PD must consider not only how dopamine acts on striatal neurons but also how to deliver dopamine to those neurons and not others. Similarly, DBS must address not only the effects of electricity on the neural elements responsible for its therapeutic effect but also the ability to stimulate only the desired neural elements. Thus, one principle of providing effective therapy is to differentiate between stimulation characteristics that relate to effective stimulation of the responsible neural elements and those characteristics related to getting the electricity there. As described later, electrical current/voltage, pulse width, and frequency primarily relate to stimulating the neural elements effectively. Electrical current/voltage and the combination of active electrodes—for example, monopolar versus bipolar configurations—relate to getting the current to the right neural elements.

The therapeutic mechanisms of action of DBS are unknown (Montgomery and Gale, 2008). However, the general consensus is that DBS activates neural elements, whether axons or the termination of the axons in the presynaptic terminals. The activation results in the generation of an action potential, which is the basic unit of information in the brain (see Chapter 11). Therefore, knowing the biophysics of neuronal action potential generation is important to understanding the therapeutic mechanism of action (see Commentary 3.1).

Key to activating the neural elements is to produce an action potential. The action potential is caused by flow of electrical charges across the neuronal cell membrane that change the voltage across that membrane. Moreover, the timing of the action potentials must be strictly controlled so as to properly encode information. These events impose certain requirements of the neuron. First, there must be some force that will move the electrical charges. This is analogous to the electromotive force or voltage in an electrical battery. Second, this flow must be precisely controlled, and this is analogous to an electrical switch in an electrical circuit. Each neuron is like a battery in which there is a relatively positive pole and a relatively negative pole (Figure 3.1). Separating electrical charges creates the battery. Such separation gives rise to forces that can be put to work, such as driving electrical appliances or generating action potentials (Figure 3.2).

As opposed to electrons, the electrical charges are mediated in the brain by ions, such as the positive sodium (Na^+) and potassium (K^+) ions and negative chloride (Cl^-) ions. The neuron pumps Na^+ ions outside its membrane, creating a greater number of positive ions outside the neuron than inside (Figure 3.3). As a result, the inside of the neuron has negative voltage relative to the outside.

Commentary 3.1 ***Sorting out DBS and Pharmacotherapy***

Although most patients with Parkinson's disease who have undergone STN DBS can substantially reduce their medications, few are able to discontinue them. Consequently, you must manage the postoperative pharmacology as well as the DBS, especially in patients who receive benefit from both therapies, such as patients with Parkinson's disease.

In the case of Parkinson's disease, when DBS proves difficult to optimize, many providers resort to pharmacotherapy. However, this strategy is not likely to work well with DBS patients, who, by definition, have not been helped by medications. Furthermore, studies demonstrate that DBS has greater efficacy than best medical therapy. Consequently, for some providers, resorting to medications represents a retreat from DBS. The goal of DBS should not necessarily be to eliminate the patient's medications, and the inability to eliminate them should not be a rationale for limiting aggressive attempts at postoperative DBS management.

Because DBS and medications can have synergistic symptomatic effects, aside from side effects that are clearly medication related, choosing which therapy to modify can be difficult. One approach is to gauge how much the patient depends on medications. Great dependence suggests suboptimal DBS settings. One indication of dependence is fluctuations in the patient's symptoms. Sometimes, such fluctuations can be detected by comparing the patient's best and worst functional states. Marked differences suggest a dependence on medications because pharmacological effects vary with plasma half-life, whereas DBS effects are usually sustained. Another way to assess dependence is to ask patients or caregivers how they know when it is time to take the medications. If the answer is that they have to look at the clock, then clinical fluctuations are probably minimal, implying that the patient is not depending on medications, the medications are having only a minimal effect, or both.

Another approach is to ask patients about the symptoms they experience in the morning, before they take the first dose of their medications. Presumably, medication effects are minimal at this time, so the degree of symptomatic control should better reflect DBS effects. Marked symptoms on awakening in the morning suggest that DBS settings are not optimal.

Most important, there is a difference in chemical concentrations of the Na^+ and K^+ ions. This provides a force analogous to the electrical forces previously described for the battery and would drive Na^+ ions into the neuron and K^+ ions out if the "switch" blocking the flows of these ions were "closed." As shown in Figure 3.4, "closing the switch" and completing this simple electrical circuit causes electrons to flow from the negative pole through the light bulb to the positive pole, turning on the light. In the case of the neuron, closing the switch and allowing, in this case, Na^+ ion current to flow through the membrane is accomplished by changes in channels in the

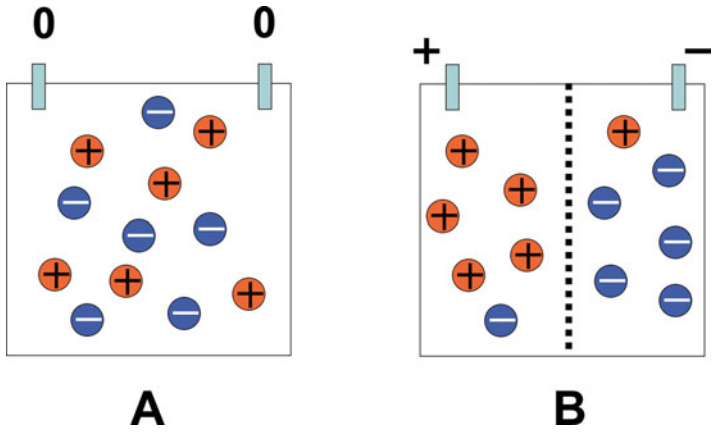

FIGURE 3.1. *An electrical battery requires a separation of electrical charges, in this case mediated by positively and negatively charged ions in the battery. When there is no separation (A), the positive and negative charges balance each other out, producing 0 V at the battery terminals. However, if a barrier is inserted and the positive ions are pumped to one (left) side and the negative ions pumped to the other (right) side, then the left side will be relatively positive and the right side relatively negative.*

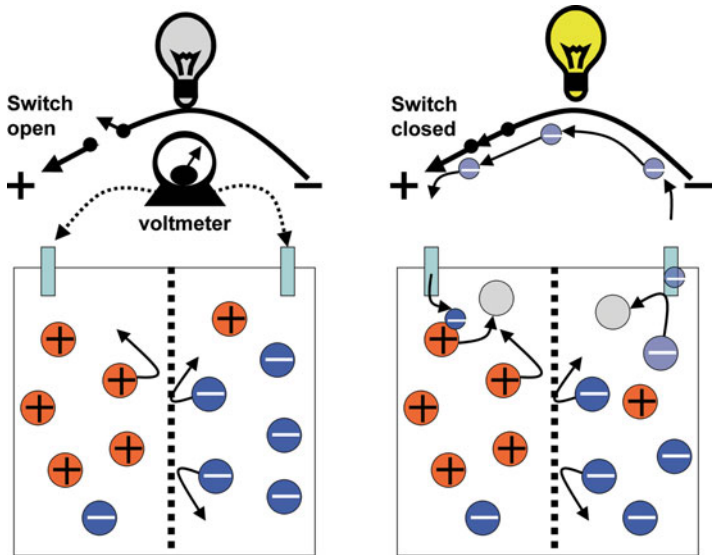

FIGURE 3.2. *There are two forces that drive the different ions to the other side. First, there is a difference in concentration in the different ions on each side of the semipermeable membrane. This difference results in a force that tries to move the ions to produce equal concentrations on each side of the barrier. The second force is electrical, as like electrical charges repel and unlike charges attract. This results in a force that wants to move the positive ions to the right and the negative ions to the left. This force is the electromotive force and can be measured by a voltmeter in volts. The electrical force can be used in electrical devices such as a light bulb. The electrical force can move electrical charges through the light bulb to produce light if the switch is closed. When the switch closes, the negative ions give up an electron that flows through the light bulb, through the closed switch, and to the positive ions on the other side of the semipermeable membrane.*

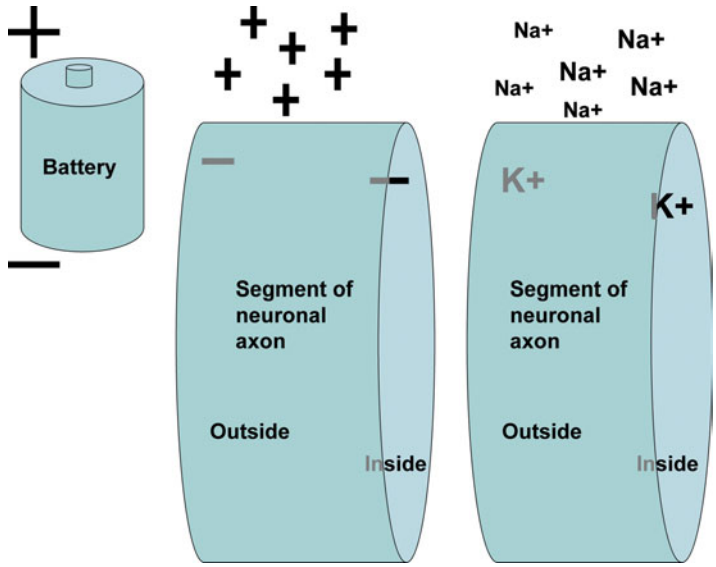

FIGURE 3.3. *Neurons, like batteries, have a relatively positive and a relatively negative poles. In this case, the two ions that are responsible for the neuronal battery are Na^+ and K^+ ions. The number of positive sodium (Na^+) ions is greater outside the neuron than inside, making the outside of the neuron relatively more positive than the inside. Conversely, there are more potassium (K^+) ions inside than outside, making the inside of the neuron more positive than the outside. At first glance, the effects of the different Na^+ and K^+ ions would balance each other out. However, more Na^+ ions are pumped out than K^+ ions are pumped in. Consequently, the greater number of positive ions outside the neuron causes the voltage inside of the neuron to be negative.*

membrane. Note that for other neurons and in other circumstances, other ions are involved, such as calcium (Ca^{2+}) and chloride (Cl^-) ions.

Activating the neural element requires closing the circuit to allow electrons to flow through the membrane. Whereas electrons flow through copper wire, electrically charged ions flow through neurons. Activating neural elements, such as axons, generates action potentials that are then conducted to neurons elsewhere in the brain. Turning on a light bulb (see Figure 3.4) is analogous to generating an action potential. The sequence of flashing lights (action potentials) encodes information (or misinformation), just like Morse code. Neurons convey and process information by the sequence of action potentials they receive. When used to treat disease, DBS may be acting to control misinformation in the activities of the neurons affected by disease. Therefore, for DBS to work, it must close the circuit in the neural membrane to generate the action potential.

Although differences in ion concentrations inside and outside of the neuron provide the force for Na^+ ions to move into and K^+ ions to move out of the neuron, thereby producing an action potential, this process must be precisely controlled. The control mechanisms are determined by the voltage across the neuronal membrane, which is affected by the relative concentrations of ions on each side of the membrane. The control mechanisms, referred to as ionic conductance channels, are like values that are closed at rest and then open to initiate an action potential. At rest, the neuronal membrane is steady at some negative voltage, typically -60 to -70 mV. If the neuronal membrane voltage becomes less negative (a process termed *depolarization*) to a point that exceeds a threshold, the valve opens to allow the flow of ions (Figure 3.5).

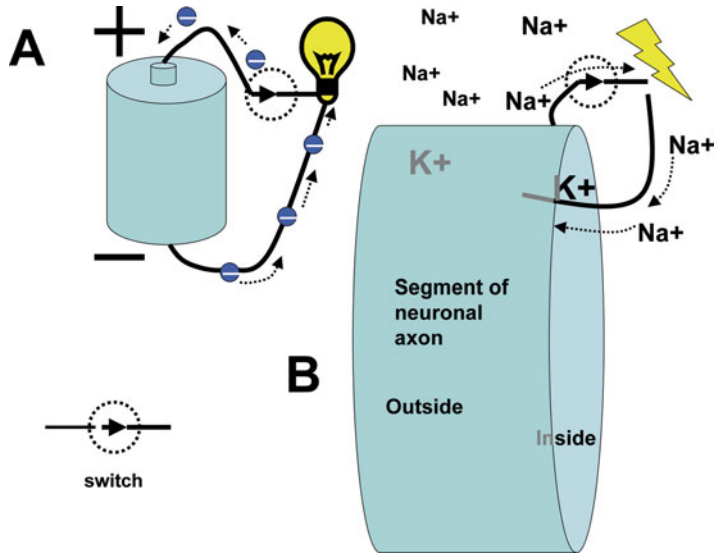

FIGURE 3.4. *Analogy between the flow of electrons in an electronic circuit powered by a battery and the flow of ions in the neuron to produce an action potential. (A) The closure of a switch allows the flow of electrical charges, in this case electrons, from the negative pole (cathode) to the positive pole (anode) going through the light bulb. The flow of electrons through the wire (high resistance) in the light bulb caused the wire to heat to white hot, thereby producing light. Similarly, closing a switch in the neuronal membrane allows* Na^+ *(in this case) to flow, thereby potentially producing an action potential.*

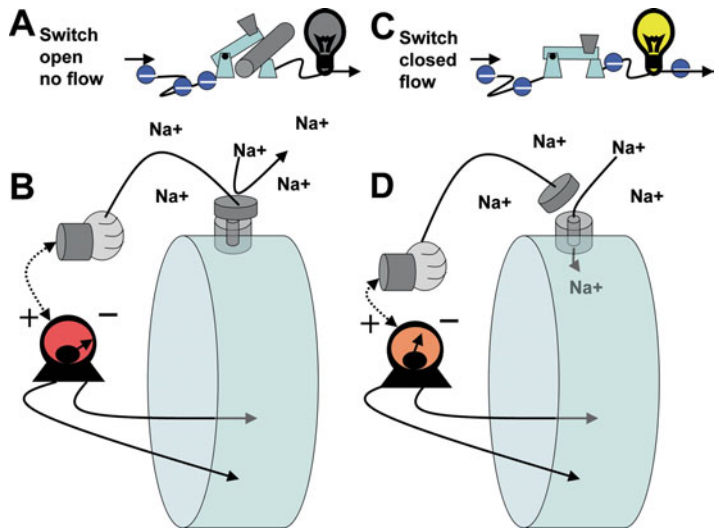

FIGURE 3.5. *Schematic representation of the "switch" in the neuronal membrane that initiates an action potential. One can visualize an electrical switch (A) in which an object (gray rod) blocks the closing of the switch, preventing the flow of electrical charges. Once the blocking object is removed (B), electrons can flow through the light bulb to produce light. Similarly, one can think of the action potential control mechanisms as a valve preventing the flow of electrical charges in the form of ions, in this case* Na^+ *ions (C). When there is a change in the neuronal membrane voltage to less negative values (depolarization) which crosses a threshold, the valve opens as if something lifts the cover of the valve thereby letting ions flow, generating the action potential (D).*

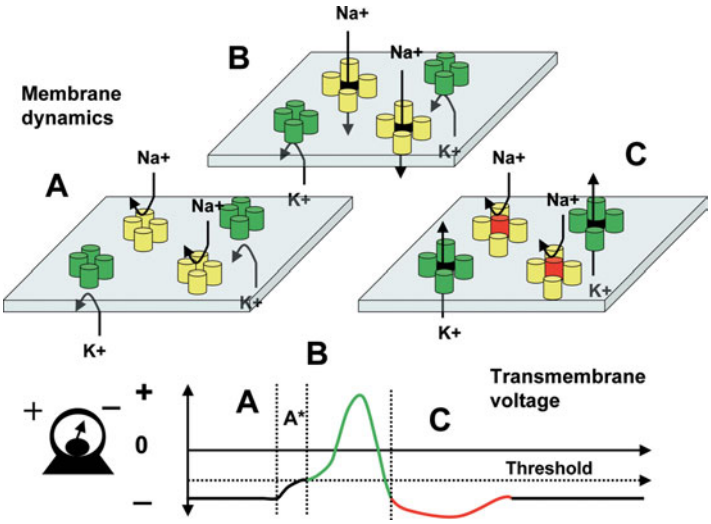

FIGURE 3.6. *Generating action potentials. During the resting state (A), the sodium (Na^+) and potassium (K^+) channels are closed, which is analogous to the membrane switch being open. This open switch prevents any flow of electrical current through the neuronal membrane and maintains the resting transmembrane potential. To generate an action potential, the transmembrane potential is depolarized or reduced to the threshold at which an action potential can be generated (A*). The depolarization can be caused by an excitatory postsynaptic potential or by administering electrical charges with DBS (see Figure 3.7). If the depolarization reaches the threshold, the Na^+ channels open, allowing Na^+ ions to move from the extracellular to the intracellular space (B). This movement furthers depolarization, resulting in the action potential. Soon after opening, the Na^+ channels become blocked so that no further Na^+ ions can move into the neuron (C), creating an absolute refractory period during which the neuron cannot generate an action potential. Also, the K^+ channels open to allow K^+ ions to move from the intracellular to the extracellular space, also reversing depolarization (C). In fact, there is an "overshoot" in which the transmembrane potential is more negative (hyperpolarized) than the resting transmembrane potential and during which the neuron is relatively refractory to any further action potentials because it would require a greater depolarization to reach the threshold. The hyperpolarization also removes the blockade of the Na^+ channels, allowing future action potentials.*

The switch in the neural membrane is created by electrical channels, made up of protein units, that in turn make up electrical channels that control the flow of ions or electrical charge across the membrane. The switch that activates neural elements is created when these channels open and allow ions or electrical charge to flow through the membrane. The transmembrane voltage, which is the difference between the positive charge outside the neural membrane and the negative charge inside the membrane, controls the switch (Figure 3.6*)*. For many neurons, the relative difference between the positive and negative charges is approximately -70 mV. If this difference is reduced to some threshold—for example, to -60 mV—the channels open, allowing ions to flow across the membrane, just as electrons move through a completed circuit. The process of reducing the voltage difference is called depolarization. DBS works by depolarizing the neural membrane.

Depolarization to activate the desired neural elements requires the delivery of electrical charge into the fluid outside the neural membrane (Figure 3.7). Thus, the outside of the neural membrane is less positive, and the difference between the outside and inside is relatively less negative; that is, the neural membrane is depolarized. Once the membrane is depolarized sufficiently to some threshold, the channels open (analogous to the switch closing) and current flows through the membrane, producing an action potential.

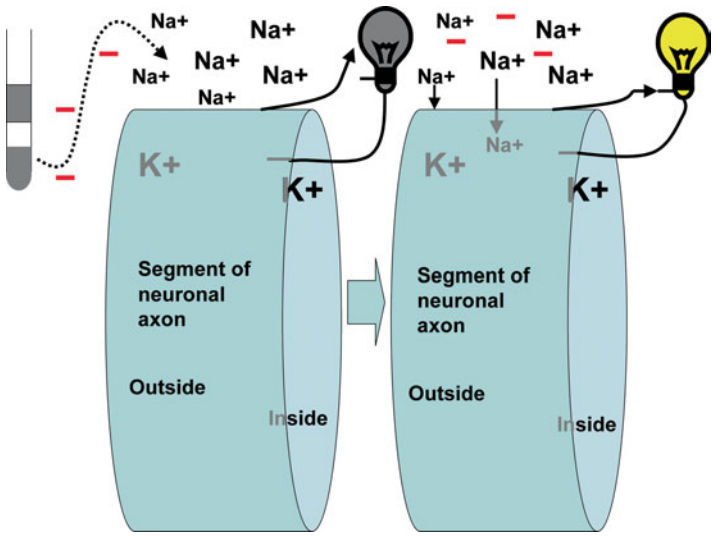

FIGURE 3.7. *Schematic representation of how DBS initiates an action potential. The negative charges emanating from the negative contact (during the cathodal phase) cause a reduction in the positive charge of the outside of the neuron (left). This reduces the neuronal membrane potential voltage across the neuronal membrane, resulting in depolarization. If the depolarization if sufficient, the ionic conductance channels open to allow the flow of ions and an action potential (right), as shown in Figure 3.6.*

For depolarization to work, electrical charges must be delivered to the neuron. Thus, the orientation of the field of electrical charges to the neuronal membrane is critically important. Electrical charges flow from the negative contact to the positive contact. Neuronal membranes perpendicular to the lines of electrical charges coming from the negative contact will receive electrical charges (Figure 3.8, neuron A). Neurons near the positive contact will not receive these electrical charges and thus will not be activated (Figure 3.8, neuron B). Likewise, neurons whose membranes are oriented parallel to the lines of electrical forces that move electrical charges will be not receive the electrical charges and, consequently, will not be activated (Figure 3.8, neuron C; Figure 3.9).

Although the orientation of the lines of electrical forces relative to the neuronal membrane (most often the axon) is important, it is difficult to know the exact orientation. Hypothetical examples are shown in Figures 3.10 and 3.11. In Figure 3.10, the axon is predominantly oriented parallel to the lines of electrical force and hence is parallel to the flow of electrical charges, so those parts of the axon would not be excited. However, the axon has a small S-shaped curve. On this small curve, the neuronal membrane is perpendicular to the lines of electrical force, so electrical charges may accumulate and may lead to depolarization of the neuronal membrane, initiating an action potential that will be conducted through the remainder of the axon. This variability of the axon's orientation limits the value of computational models of DBS, which assume a smooth and regular orientation. For example, if the axon in Figure 3.10 is straight and not curved, it will not be activated.

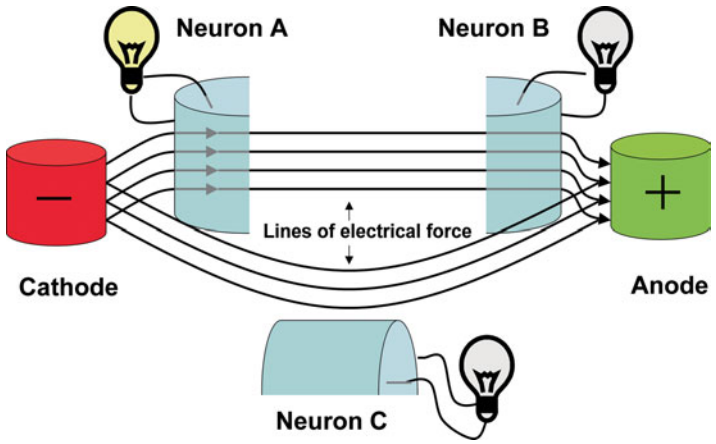

FIGURE 3.8. *The importance of the orientation of the neuronal membrane relative to the lines of electrical force coming from the negative contact. Neurons whose membrane surfaces are near the negative contact and perpendicular to the lines of electrical force (neuron A) will respond to the electrical force entering the neuron and depolarize, generating an action potential. Neurons whose membrane surfaces are near the positive contact and perpendicular to the lines of electrical force (neuron B) will not respond to the electrical force exiting the neuron, will not depolarize, and will not generate an action potential. Neurons whose membrane surfaces are oriented parallel to the lines of electrical force (neuron C) will not respond to the electrical force entering the neuron, will not be depolarized, and will not generate an action potential.*

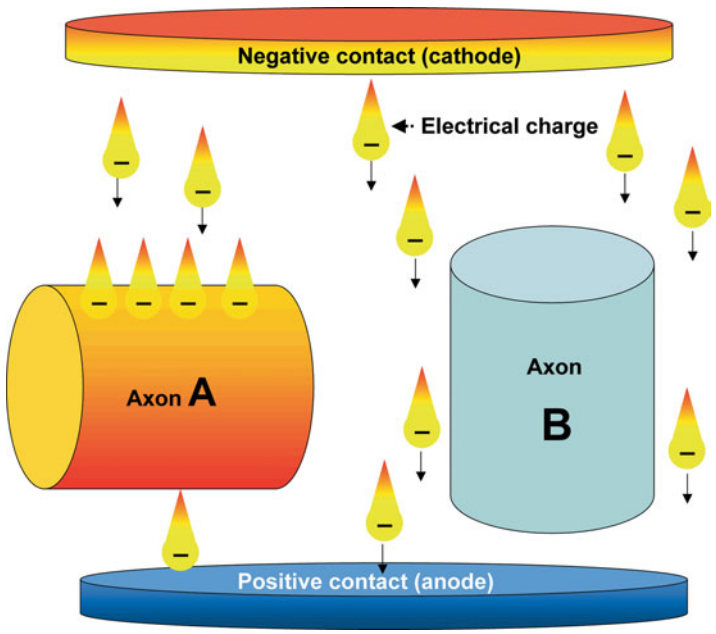

FIGURE 3.9. *Hypothetical illustration of the importance of the orientation of the neuronal membrane to the lines of electrical force from the negative contact. Negatively charged ions move from the cathode to the anode. When the neuronal membrane is perpendicular to the flow of ions along the lines of electrical force, the negative charges can be thought of as accumulating on the surface of the axon (A). When enough negative charges accumulate, the resultant depolarization exceeds some threshold and the axon responds with an action potential. When the axon (B) is parallel to the flow of the negative charges, negative charges will not accumulate on the neuronal membrane. The negative charges will continue to flow past the neuronal membrane. Consequently, electrical charge will not accumulate, the axon will not depolarize, and no action potential is created.*

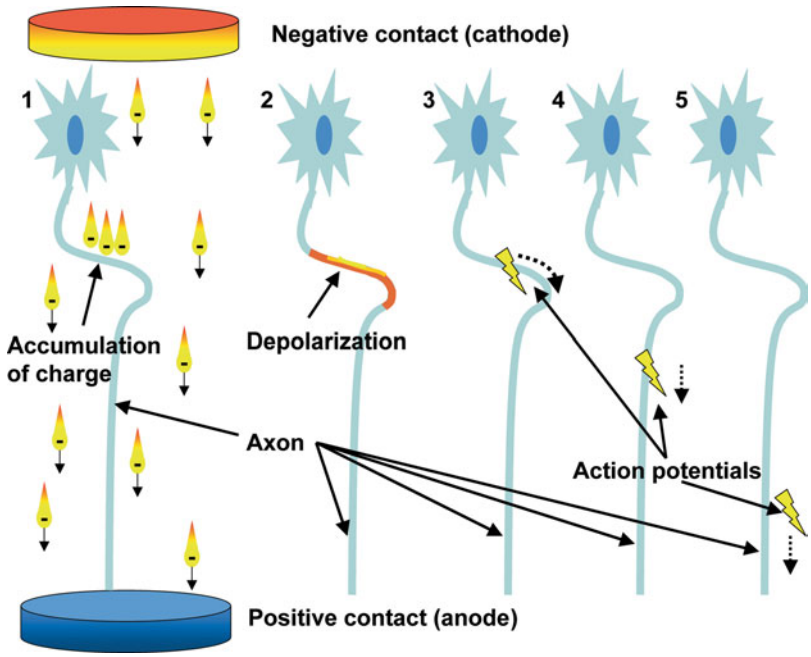

FIGURE 3.10. *A hypothetical example of how an irregularity in the shape of an axon in the electrical field may result in an unanticipated excitation of the axon over time. In this example, the axon is generally parallel to the lines of electrical force and to the flow of electrical charges. Such an orientation would not be expected to result in an action potential. However, the axon with the S-shaped curve has a small portion that is oriented relatively perpendicular to the lines of electrical force. Consequently, negative charges can accumulate on this small region, the membrane may be depolarized, and, if the depolarization is sufficient, this may result in an action potential that is conducted through the remainder of the axon.*

It is far more likely that axons have irregular shapes and, consequently, the precise orientation of the axon in the electric field cannot be predicted. Nevertheless, the orientation of the neuronal elements to the electrical field is important, as evidenced by the fact that reversing the polarity in bipolar stimulation can have a markedly different clinical effect.

A similar hypothetical situation is shown in Figure 3.11, but for the end of the axon that forms the synaptic terminal. Again, this difference in the orientation of the neuronal element could give rise to an action potential, especially because axonal terminals have the lowest excitation thresholds.

Figure 3.11 shows the action potential going in both directions. The action potential moving toward the synapse is traveling orthodromically, which is usually the case in biological systems. The action potential moving in the opposite direction, toward the neuronal cell body or soma from which the axon originated, is traveling antidromically. Although not the usual circumstance, antidromic activation should have important physiological effects and may mediate much of the therapeutic mechanisms of DBS (see Commentary 3.2). Figures 3.12 and 3.13 show the potential

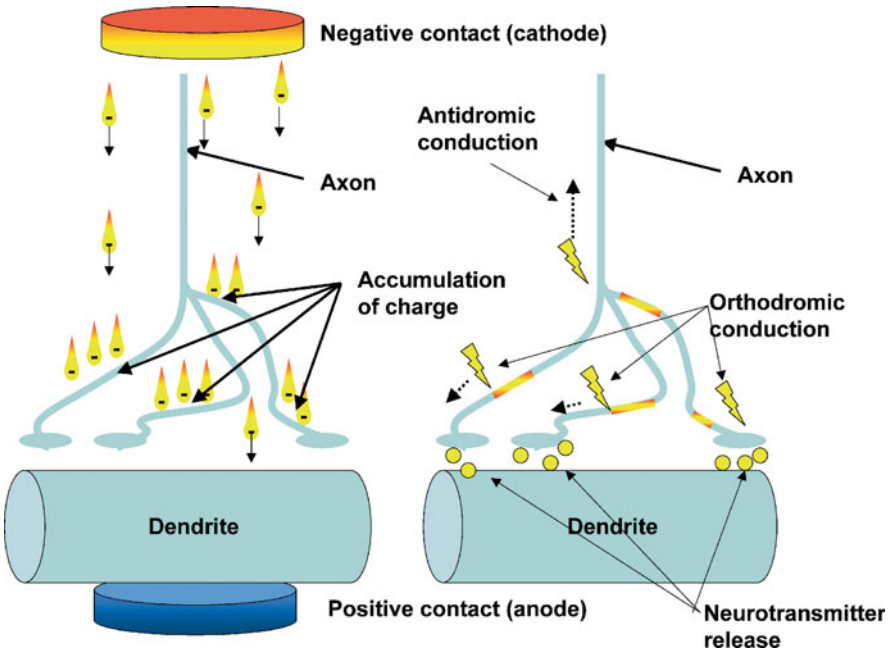

FIGURE 3.11. *A hypothetical example of how changes in the orientation of an axon branching at the synaptic terminal can give rise to excitation of the axon, even though the majority of the axon is parallel to the lines of electrical force and flow of electrical charge. Even when the axon is oriented parallel to the lines of electrical force, the axon terminal branches may be relatively perpendicular to the lines of electrical force and become charged. This charge may result in an orthodromic conduction of action potentials to the synaptic terminals, either exciting or inhibiting the postsynaptic neuronal element, in this case a dendrite. At the same time, the action potential initiated in the axon branches is conducted antidromically to excite its associated neuron, which was the origin of the axon terminals being excited.*

physiological implications of antidromic activation. In these cases, DBS of the subthalamic nucleus (STN) or globus pallidus internal segment (GPi) becomes synonymous with direct activation of the thalamus and motor cortex (see Commentary 3.2).

Neurons differ in how much electrical charge deposited by DBS is required to produce an action potential. For example, large-diameter axons require less electrical charge than do small-diameter axons. DBS programming can exploit these differences. For example, the desired DBS therapeutic effect may require activating large-diameter axons, whereas activating medium-diameter axons may cause unwanted side effects. DBS can be adjusted to activate only the larger-diameter axons without activating the medium-diameter axons. This differential response is accomplished as follows. Larger-diameter axons have a larger surface area, which means that more negative electrical charges can accumulate on the surface of the axon. This increased charge results in a greater depolarization of the neuron and, therefore, a greater probability of generating an action potential. Thus, controlling the current flow within a volume of tissue allows control of how many and which axons will be activated. For an extensive discussion of electrophysiological responses to stimulation, see Ranck (1975).

Commentary 3.2. ***Antidromic Activation as a Mechanism of DBS Action***

The precise therapeutic mechanisms of action of DBS are unknown, despite considerable and expanding knowledge of its effects on neuronal activities (see Chapter 12). Most research on the neuronal effects of DBS has focused on the local effects in the stimulated target (Montgomery and Gale, 2008). The reduction in neuronal activities in the target that has been reported in many studies is thought to reflect the activation of presynaptic terminals. Because inhibitory synapses predominate, the net effect has been to inhibit neuronal cell discharges. However, studies of neuronal activities in structures downstream from the DBS target reveal findings that are consistent with *activation* of neuronal cell discharges, raising the question of whether the inhibition in the DBS target is epiphenomenal. Thus, recordings in the thalamus reveal that DBS of the GPi inhibits thalamic neuronal activities (Montgomery, 2006), whereas DBS of the STN enhances GPi neuronal activity (Hashimoto et al., 2003; Montgomery and Gale, 2008).

Several studies have reported that DBS may antidromically activate neurons whose axons pass near the DBS target, either those en route to other structures (Montgomery, 2006) or those that terminate in the DBS target (Baker et al., 2002; Montgomery and Gale, 2008). STN DBS evoked potentials have short latencies and refractory periods that are consistent with axonal activation, suggesting antidromic activation of the cortical neurons projecting to the STN. Direct recordings of the cortex in nonhuman primates reveal a short latency and highly temporally consistent activations with STN DBS that indicate antidromic activation. These findings are consistent with the biophysical observation that axon terminals have the lowest threshold for activation (Grill et al., 2008). Studies in the rodent model of parkinsonism demonstrate the importance of antidromic activation to improve symptoms (Gradinaru et al., 2009). Similarly, recordings of thalamic neurons also show antidromic activation with GPi DBS.

Walker and colleagues (2008) found that contralateral STN DBS increased neuronal activities with latencies of approximately 2.5 ms. Their findings suggest a monosynaptic orthodromic activation of the contralateral STN neurons. One candidate pathway would be antidromic activation of the cortical neurons that project into the stimulated STN. The antidromic action potential would travel up the axon until it reached axon collaterals. The action potential would then precede orthodromically down the axon collaterals and terminate at neurons in the contralateral STN. Walker and colleagues also found direct antidromic activation of STN neurons with DBS of the contralateral STN (H. Walker, personal communication). This mechanism could explain the ipsilateral clinical benefit often seen with unilateral STN DBS.

The feature common to therapeutic DBS for patients with Parkinson's disease, regardless of whether the VL, GPi, STN, or motor cortex is involved is direct activation of the cortex, (Benvenuti et al., 2006), whether the activation is antidromic or monosynaptic and orthodromic. Alternatively, there

(*continued*)

Commentary 3.2 ***(continued)***

could be as many different therapeutic mechanisms as there are DBS targets, or there could be one or only a few mechanisms that are common to all targets. The principle of parsimony suggests that direct activation of the cortex is the most likely therapeutic mechanism.

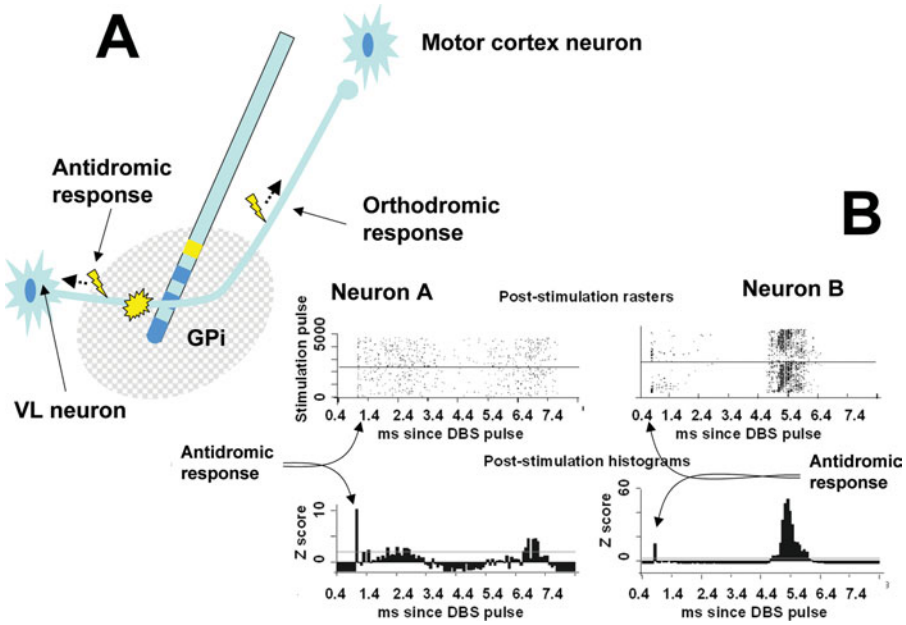

FIGURE 3.12. *The consequences of initiating an action potential in axons passing near the DBS target. In this case, research has shown that GPi DBS activates axons from the ventrolateral (VL) thalamus, causing antidromic activation of the thalamic neurons (Montgomery, 2006), as shown in A and Figure 3.11. Evidence for antidromic activation of two VL neurons is shown in B. The top figures in B are post-stimulus rasters that show the discharge of the neurons in the approximately 8 ms after each DBS pulse, which occurs at time 0. Each row represents the neuronal response to the DBS pulse, and each dot represents the discharge of the neuron. The responses in the rasters are then organized and summed in columns for increments of time to construct the histograms that show the average response over time after the DBS pulse. The very short latency (approximately 1 ms) is highly consistent with an antidromic response [for further evidence of the antidromic response, see Montgomery (2006)]. The action potential generated in the axon of the thalamic neuron passing near the GPi could be expected to result in an orthodromically conducted action potential, in addition to the antidromically conduction potential. This orthodromically conducted action potential could then monosynaptically activate the motor cortical (and other cortical) neurons, as shown in A. All thalamic neurons recorded in this study show a reduction of reduced activity approximately 3.5 ms after the GPi DBS pulse (delivered at a high frequency), which is consistent with DBS activating the output of the GPi and not inhibiting the segment, as some current theories of DBS hold. Also striking for these two neurons and other thalamic neurons is the remarkable and robust increase in thalamic neuronal activity after the GPi DBS-induced inhibition. This postinhibitory rebound activity is seen in both neurons. Neuron B displays two components of increased activity, including a very large later increase that is thought to reflect reentrant activity from the cortical neuron that was monosynaptically activated by action potentials generated in the thalamic neuronal axons passing near the GPi DBS. The robust postinhibitory rebound of increased excitability of the VL neurons calls into question the basis for most current theories of basal ganglia physiology and pathophysiology. (Adapted from Montgomery, 2006.)*

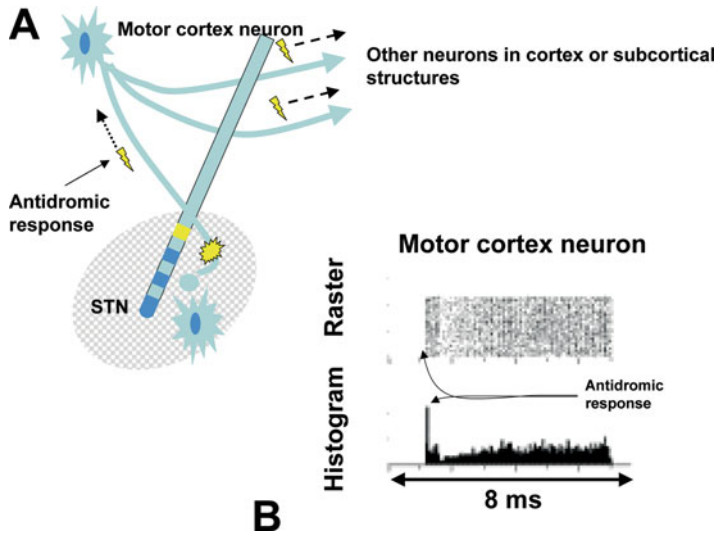

FIGURE 3.13. *An example of the consequences of initiating an action potential in axons passing near the DBS target. In this case, research has shown that STN DBS antidromically activates axons from the cortex, which synapses in the STN (Montgomery and Gale, 2008), as shown in A. The evidence for a motor cortical neuron is shown in B. The top figure in B is the post-stimulus rasters that reveal the neuronal discharges of the neurons approximately 8 ms after each DBS pulse, which occurs at time 0. Each row represents the neuronal response to the DBS pulse, and each dot represents the discharge of the neuron. The responses in the rasters are then organized and summed in columns for increments of time to construct the histograms that show the average response over time after the DBS pulse. The very short latency (approximately 1 ms) is highly regular, as evidenced by the tall and narrow response at approximately 1 ms, which is consistent with an antidromic response. The action potential generated in the axon terminal of the motor cortical neuron could be conducted antidromically toward the cortex. This action potential would then pass orthodromically down the collateral axons of the same neuron to the synapses on other neurons in the cortex, to other subcortical structures, or both. Thus, the effects of STN DBS are rapidly conducted widely throughout the brain, contrary to many theories of DBS that focus exclusively on local DBS effects. (Adapted from Montgomery and Gale, 2008.)*

Controlling the Flow of Electrical Charges

The shape and distribution of the electrical fields created by the electrical current/voltage are very important. These electrical fields are the spatial distribution of the current or flow of electrical charges. The size, shape, and gradient or intensity of an electrical field can be greatly affected by the configuration of active electrical contacts. This principle can be exploited to provide DBS management of symptoms. Four electrical contacts on the typical DBS lead provide a large number of combinations of active contacts and, therefore, a large number of different fields of electrical current.

Generally, the combinations of active electrical charges can be divided into monopolar or multipolar, which are defined according to the number and nature of active contacts within the DBS target. *Monopolar* refers to only negative contacts (cathodes) within the stimulated structure. The positive contact (anode) in monopolar stimulation is the IPG itself, which is typically placed under the skin over the chest. From an electrical standpoint, the positive contact on the pulse generator is an infinite distance from the negative contact in the brain; hence, the stimulation of the brain can be considered as coming from a single electrical contact. *Multipolar* configurations have more than one active contact within the stimulated structure,

and these necessarily include both negative and positive contacts. A bipolar configuration could have a single negative and a single positive contact in the DBS target. The allowable combinations of negative and positive contacts may vary by manufacturer, and the reader is referred to the manufacturers' information.

The intensity, shape, and distribution of the electrical current field are strongly influenced by the spatial relation between the negative and positive contacts and the nature of the brain tissue between them. With constant-*voltage* IPGs, the size and intensity of the electrical fields also depend on the impedance of the tissue between the negative and positive contacts. For both monopolar and multipolar configurations, the current flow is greatest next to the negative contact and diminishes as the neural element is farther away from the negative contact. However, in monopolar configurations, the current flow falls off as the distance from the negative contact increases:

$$\text{Electrical charge}_{\text{monopolar}} \propto 1/r \tag{3.1}$$

where r is the distance of the neural element from the negative contact. Thus, doubling the distance from the contact halves the electrical current. For bipolar configuration, electrical current is reduced by the square of the distance to the negative contact but is increased by the square of the distance between the negative and positive contacts:

$$\text{Electrical charge}_{\text{bipolar}} \propto d^2/r^2 \tag{3.2}$$

Although the fact that the electrical charge increases with the distance between the anode and cathode (d) is counterintuitive, this fact has implications for the choice of DBS leads based on the spacing between electrodes. To maximize the intensity of the electrical field to ensure efficacy, one would want a DBS lead with widely separated contacts. On the other hand, wider spaced contacts makes it more difficult to finely tune the distribution of the electrical field in the long axis of the DBS lead, which might be needed to minimize side effects. Of the two currently available DBS leads, I prefer the lead with the wider spacing.

Often, it is helpful to think of electrical fields as lines of electrical force that radiate out from the negative contact (Figure 3.14). In monopolar configurations, the lines of electrical force radiate outwards in all directions. In bipolar configurations, the lines of electrical force radiate out from the negative contact but are attracted to the positive contact. Thus, in bipolar configurations, the lines of electrical force are bent inwards and concentrated.

One could represent the strength of the electrical fields by counting the number of lines of electrical force per unit volume (see Figure 3.14). Thus, a box placed near the negative contact will have many more lines of electrical force than a box placed at a distance from the negative contact. In bipolar stimulation, the positive contact placed at a greater distance allows for more lines of electrical force at greater distances from a line connecting the negative and positive contacts (see Figure 3.14B) compared to a closer positive contact (see Figure 3.14C). Thus, the intensity of the electrical fields a given distance from the negative contact will be less when the negative and positive contacts are adjacent (narrow bipolar) than when they are separated (wide bipolar).

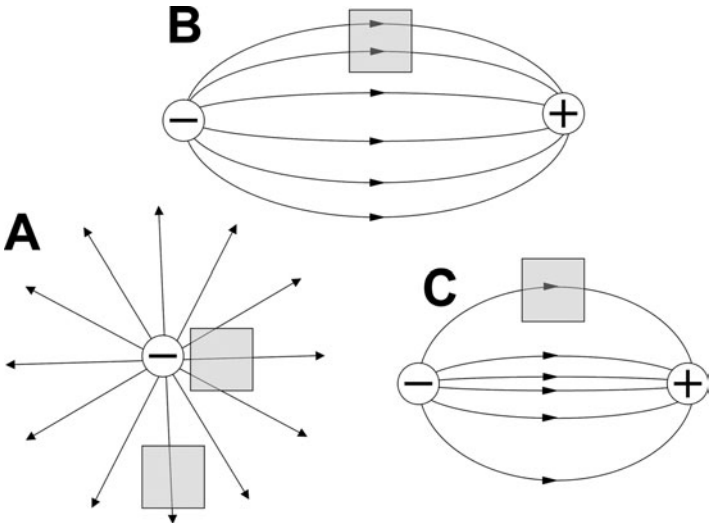

FIGURE 3.14. *The electrical field can be pictured as lines of electrical forces emanating from the negative contact. In the case of monopolar stimulation (A), the lines of electrical force radiate out in all directions. In the bipolar configurations (B and C), the lines of electrical force radiate from the negative contact but are attracted to or pulled in by the positive contact. Thus, the shape or spatial distributions of the electrical fields are different. The strength of the electrical field in any spatial location can be inferred from the lines of electrical forces traversing that volume (boxes). In the case of monopolar stimulation, the intensity of the electric field is greater near the negative contact and rapidly diminishes as the box moves out. Figure B shows the hypothetical case of a wide bipolar configuration where there is a large distance between the cathode (negative) and anode (positive) contacts. Figure C shows the case of narrow bipolar configuration where the distance between the cathode (negative) and the anode (positive) contacts is smaller. Note that as drawn, the intensities of the electric fields produced by widely separated negative and positive contacts (wide bipolar; B) are different from those produced by closer spaced negative and positive contacts (narrow bipolar; C). For the same volume of space, represented by the box, the intensity is greater with the widely separated contacts (B) compared to the closer spaced contacts (C). One could describe this as follows: The closer positive contact produces a greater attraction for the lines of electrical force emanating from the negative contact, thus bringing the lines of electrical force closer to the line connecting the negative and positive contacts but less further out where the neural elements lie.*

Equations (3.1) and (3.2) indicate that the shapes of the electrical fields are different and depend on the configuration of the active electrodes. A hypothetical example is shown in Figure 3.15, which plots the relative intensities of the electrical fields as a function of distance from the negative contact and electrode configuration, with 1 unit of electrical current/voltage (e.g., 1 mA or 1 V). Consider the circumstance of a narrow bipolar where adjacent contacts are used compared to when the negative and positive contacts are separated by one unused contact. For the same electrical current/voltage, the intensity of stimulation with the narrow bipolar configuration is less than that of the wide bipolar configuration. The intensity of the electrical field falls off rapidly with bipolar stimulation. The intensity of monopolar stimulation closer to the negative contact is less, but it does not decrease as rapidly as the distance from the negative contact increases.

The effects of electrode configuration on electrical current are illustrated in Figure 3.16. The electrical charge from the negative contact flows to the positive contact. Imagine the flow of electrical charge as water flowing between the spigot (the negative contact) and the drain (the positive contact). For monopolar stimulation, the drain effectively is very far away. Having a different number of drains (positive anodes) in different configurations and relatively close to the spigot (the negative cathode) is

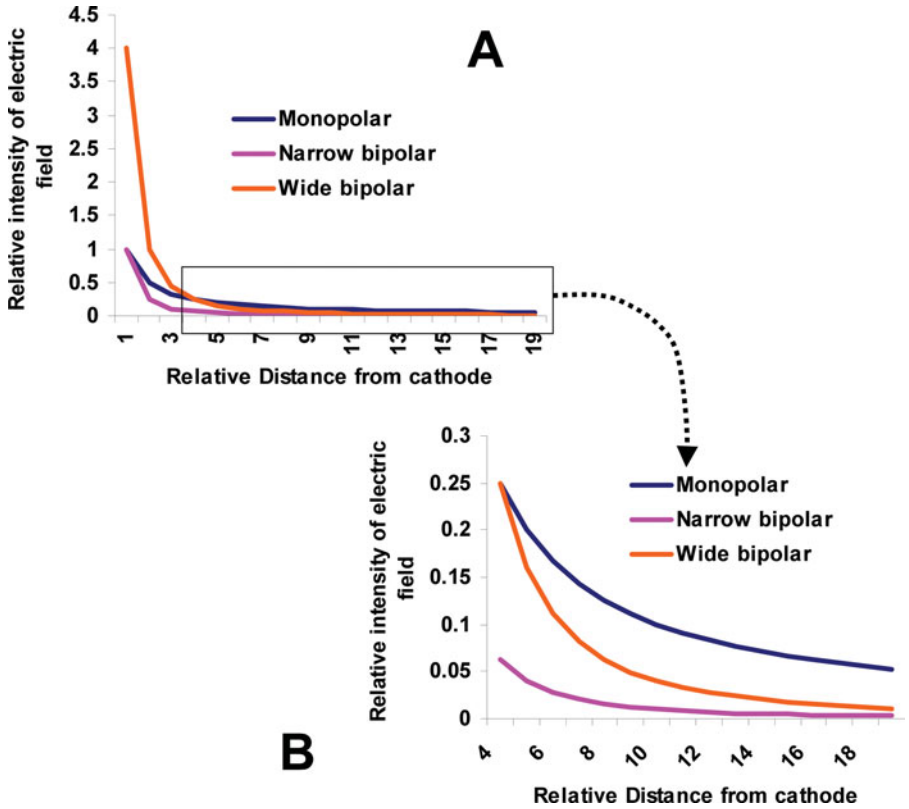

FIGURE 3.15. *Hypothetical example of how the intensity of the electrical field decreases at increasing distances from the negative contact for monopolar, narrow bipolar (1 unit of separation between cathode and anode), and wide bipolar (2 units of separation) stimulation. The wide bipolar configuration provides the highest intensities near the negative contact (A), but the intensity falls off rapidly, such that at 4 units of distance the intensity of the wide bipolar configuration is less than that of the monopolar configuration (the box in A is expanded in B). The narrow bipolar configuration produces the electrical field with the smallest volume and the least intensity.*

analogous to multipolar stimulation. A bipolar configuration is one in which there is a single spigot (a negative contact or cathode) and a single drain (a positive contact or anode) that are relatively close together. Here we have considered two cases—wide bipolar and narrow bipolar stimulation—but the same concepts apply to any multipolar configuration.

An analogy for monopolar stimulation would be water flowing onto a table without a drain. It would cover in all directions. The water would cover a large area but not to a great depth. The consequence would be activating larger-diameter axons at a large distance from the negative contact. However, the current would not be very high and would create a smaller charge density or electrical intensity (see Figure 3.16). In a bipolar configuration, a drain would attract and focus the water, covering a smaller area but to a greater depth, which corresponds to a greater electrical charge density.

The analogy of flowing water to the flow of electrical current also helps illustrate why wide bipolar stimulation generates more intense, and therefore more effective, activation of axons (Figure 3.17). Water and electrical charges will be attracted to the

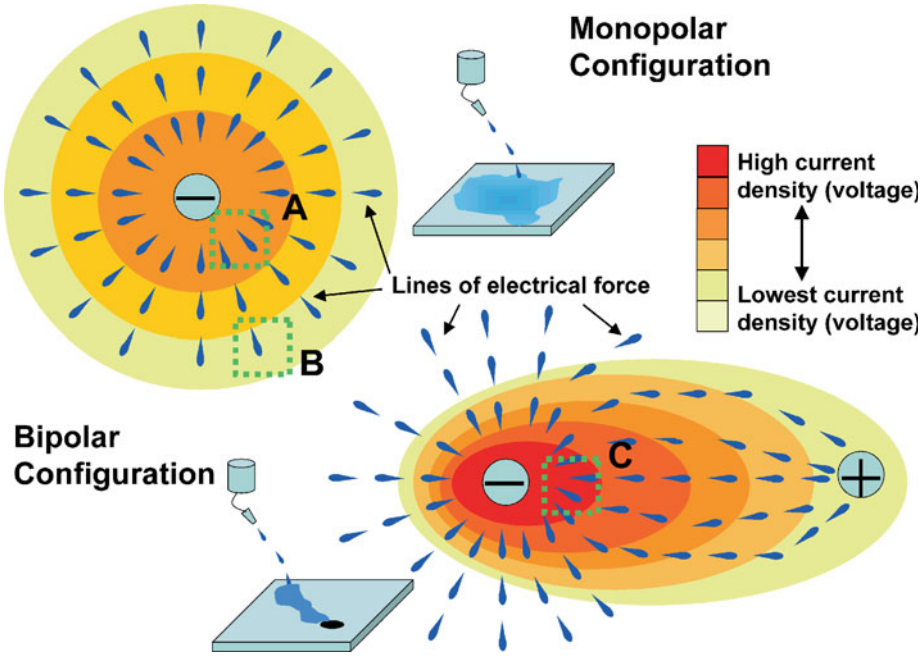

FIGURE 3.16. *The effects of electrode configuration on electrical current. The electrical charge from the negative contact flows to the positive contact. Imagine the flow of electrical charge as water flowing between the spigot (the negative contact or cathode) and a table where there is no drain, which is analogous to monopolar stimulation in which the IPG is the anode (positive) contact, or when there are several drains (positive anodes) in different configurations relative to the spigot (negative cathode), as there are in multipolar configurations. In the monopolar configuration, the water will spread out over the table and cover a large area, but not to any depth. Thus, in monopolar stimulation, the electrical current will be widely distributed, but the electrical current density (measured in microcoulombs per surface area of the electrical contact during each phase of the DBS pulse) will not be great. In the bipolar configuration, the electrical current will be less widely distributed, but the electrical current density will be concentrated and consequently, greater.*

drain, and electrical charges going down the drain rather than through the neuronal membrane will reduce the amount of electrical charge on the neuronal membrane that is necessary to activate the axon. When the drain or positive contact is near the spout or negative contact, such as in a narrow bipolar configuration, more water or electrical charge will go into the drain or positive contact than can get onto the neuronal membrane. When the drain or positive contact is farther from the spout or negative contact, as it is in a wide bipolar configuration, more electrical charge will be applied to the neuronal membrane to activate the axon. Figure 3.18 schematically shows the various electrical fields that can be generated by different electrode configurations.

Current Intensity in Monopolar and Bipolar Electrode Configurations

As described previously, the strength of the electrical field diminishes as the distance from the negative contact increases. However, the strength falls off more rapidly in bipolar stimulation than in monopolar stimulation. For example, the strength of the electrical field created by monopolar stimulation is reduced by one-half at double the distance from the negative contact, but that created by bipolar stimulation is reduced to one-fourth at double the distance from the negative contact. However, the

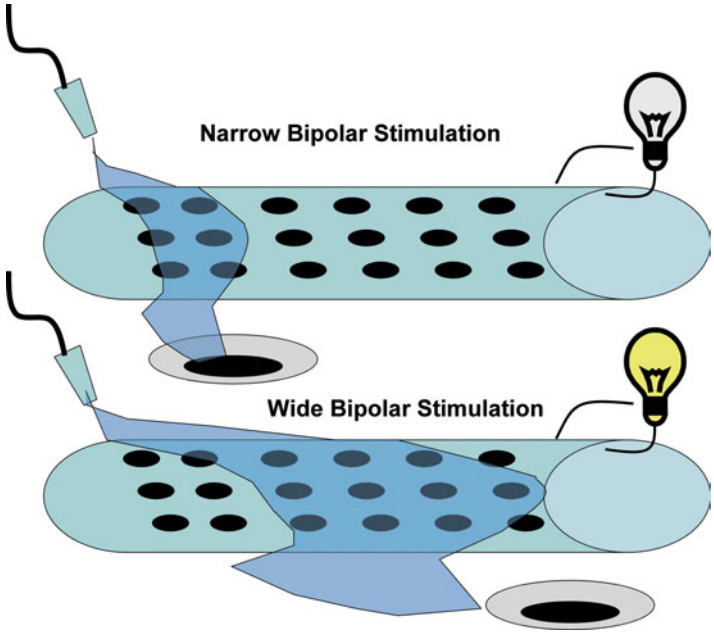

FIGURE 3.17. *The effects on wide versus narrow bipolar stimulation of neuronal axons. With narrow bipolar stimulation, more electrical charges are drained away before activating the axons than are drained with wide bipolar stimulation. Thus, wide bipolar stimulation will be more effective in activating action potentials.*

strength of the electrical field created by bipolar configurations increases by the square of the distance between contacts. Thus, wide bipolar configurations generate a more intense electrical field close to the negative contact than do narrow bipolar configurations. Narrow bipolar configurations will generate a stronger electrical field than will monopolar stimulation. One way to visualize the difference between wide and narrow bipolar stimulation is represented in Figure 3.18. The monopolar stimulation will create a larger but less intense electrical field.

The differences in shape, size, and intensity generated by the different electrode configurations can be exploited to maximize the efficacy and minimize side effects of DBS. For example, monopolar stimulation of electrodes too close to the internal capsule, medial lemniscus, optic tract, or oculomotor fibers increases the chance of electrical charge reaching and activating axons in these structures, causing side effects.

Suppose that the therapeutic effect depends on the number of large activated axons (Figure 3.19A). In this case, monopolar stimulation at a current/voltage low enough not to stimulate axons in the internal capsule activates only two axons in the STN or GPi. Increasing the current/voltage increases both the size and the intensity of the electrical field (Figure 3.19B), increasing the number of axons activated in the STN or GPi to three, thereby increasing efficacy. Higher current/voltage stimulation, however, would also activate axons in the internal capsule, producing unwanted muscle contractions. In this case, changing to a wide bipolar configuration (Figure 3.19C) activates more axons (three) in the STN or GPi, increasing efficacy but without activating the axons in the internal capsule that cause muscle contractions.

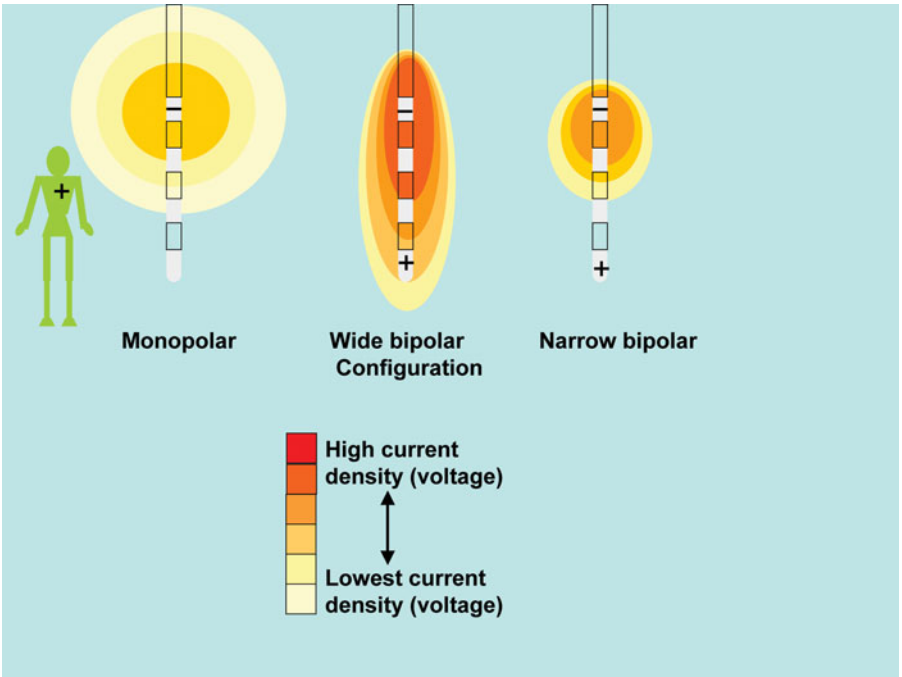

FIGURE 3.18. *Schematic representation of the different sizes, shapes, and intensities of electrical fields generated by different configurations of active contacts. The monopolar configuration provides the largest volume of electrical fields, but they are less intense than those provided by bipolar stimulation. The wide bipolar configuration results in larger and more intense electrical fields than does the narrow bipolar configuration because the electrical field intensity is directly related to the square of the distance between the cathode and anode squared (to the second power; see E. 3.2).*

Why not use wide bipolar stimulation all the time? Consider the example in which the electrode is not too close to the internal capsule (Figure 3.19D). Monopolar stimulation would activate more (four) axons in the STN or GPi rather than only the three axons activated by the wide bipolar configuration.

The key concept is that the size, shape, and intensity of the electrical fields can be tailored to the patient's unique anatomy relative to the location of the DBS electrodes. Controlling the size, shape, and intensity of the electrical fields allows you to maximize benefit and minimize side effects.

Figures 3.20 through 3.22 show various monopolar and bipolar configurations. By carefully selecting electrode configurations, currents/voltages, and pulse widths, you can control which regions of the anatomy surrounding the DBS negative contact are excited. Conceptually, this situation is no different than selecting a particular formulation of levodopa, such as immediate-release or controlled- or extended-release carbidopa–levodopa for Parkinson's disease. Different doses of levodopa in the carbidopa–levodopa preparation are analogous to the current/voltage used in DBS. Similarly, the use of multipolar configurations to constrain the size and shape of the electrical fields to control the regions affected is analogous to the adjunctive use of carbidopa to restrict the actions of levodopa to the brain rather than involving the rest of the body. Another useful analogy is the use of dopamine agonists with varying

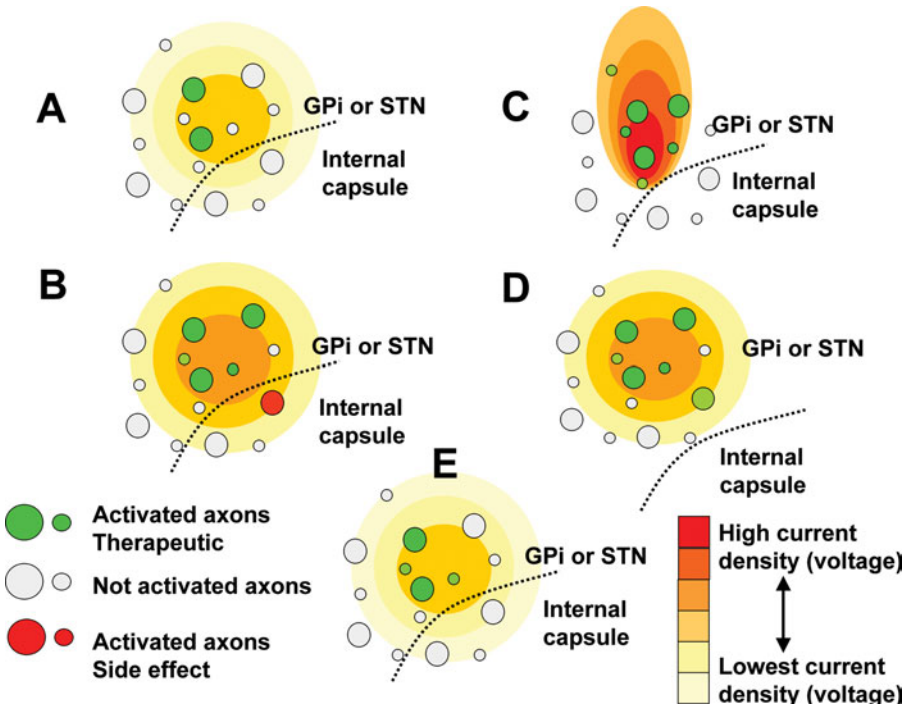

FIGURE 3.19. *The differential effects of monopolar and bipolar stimulation. Here, effectiveness is determined by the number of axons activated within the STN or GPi, and side effects are caused by activation of axons in the internal capsule. Hypothetical examples A, B, C, and E show the DBS electrode too close to the internal capsule. Stimulation spreading to the internal capsule would result in unwanted muscle contractions. Lower current/voltage monopolar stimulation would not activate axons in the internal capsule but would be less effective because it activates only two representative axons (A). Increasing the current/voltage would increase the spread and intensity of the electrical field, thereby increasing effectiveness by activating three axons in the STN or GPi (B). However, this increase also activates the internal capsule, causing muscle contractions. Switching to a wide bipolar configuration creates a smaller but more intense electrical field. Consequently, no axons are activated within the internal capsule and, therefore, there are no side effects (C). In addition, effectiveness is greater because three representative axons are activated in the STN or GPi. However, wide bipolar stimulation is not always the most effective. For example, when the cathode (negative) contact in the DBS lead is farther away from the internal capsule, monopolar stimulation activates more axons—in this case, four representative axons in the STN or GPi—without activating axons in the internal capsule, thereby avoiding the side effect of muscle contractions (D). Figure E shows the effects of using the smaller current/voltage as shown in A but with a longer pulse width, which results in more axons in the target being activated but without axons in the internal capsule being activated. However, a wider pulse width will increase the rate at which electrical charge is removed from the battery.*

degrees of specificity for D_1 and D_2 receptors, which is conceptually similar to the use of pulse widths and currents/voltages to select axons of different sizes.

Two commercially available IPGs provide for nearly simultaneous delivery to two stimulus trains (called groups). The two trains have the same frequency but are offset (phase delay) so that the stimulus pulse in one group follows the stimulus pulse of the second group and they do not overlap (Figure 3.23A). The two groups can vary in current/voltage, pulse width, and polarity but not frequency (rate). Thus, each group can be associated with a different electrical field (Figures 3.23B and 3.23C). Theoretically, the two groups could give an effective electrical field that is some combination of the two (Figure 3.23D). This could be an advantage in shaping the electrical field for greater efficacy and fewer side effects. For example, the stimulation through the most ventral lead produces the greatest efficacy but more side effects. In

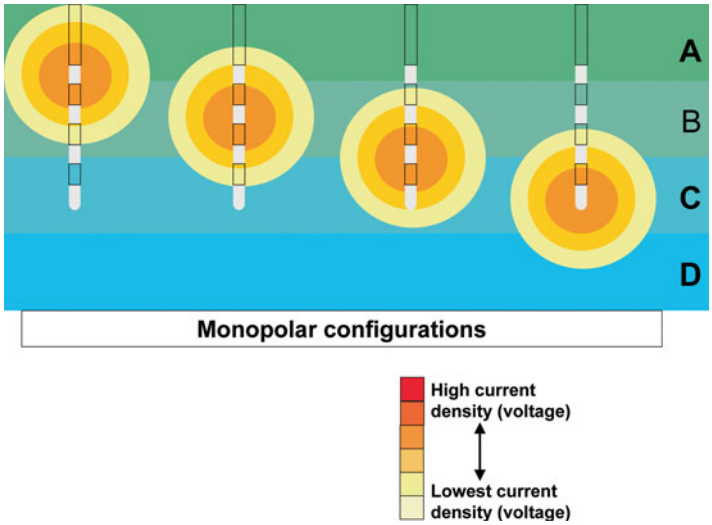

FIGURE 3.20. *Schematic examples of relative distributions of electrical fields generated by various configurations of monopolar stimulation in the vertical direction (long axis of the DBS lead).*

this case, the electrical field generated around the most ventral contact would have to be small. Stimulation through a more dorsal contact could be effective but less so than stimulation through the most ventral contact; it may also be associated with fewer side effects and thus could have a larger electrical field. It is possible that a synergistic combination of both fields could further increase the efficacy without increasing the side effects.

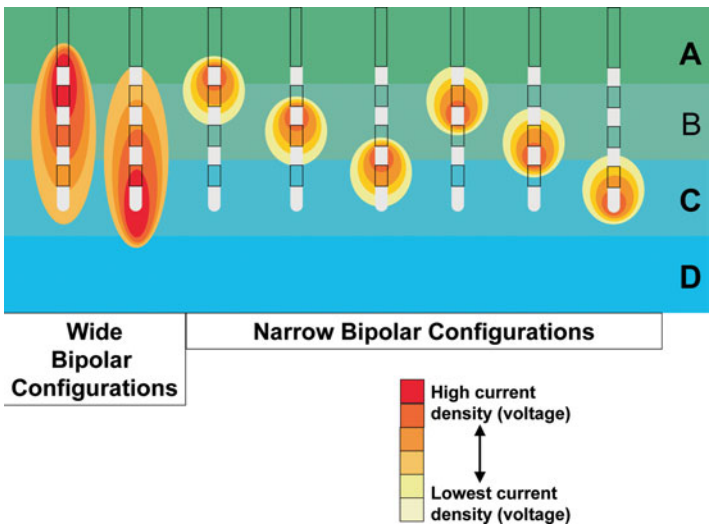

FIGURE 3.21. *Schematic examples of relative distributions of electrical fields generated by various configurations of bipolar stimulation in the vertical direction (long axis of the DBS lead).*

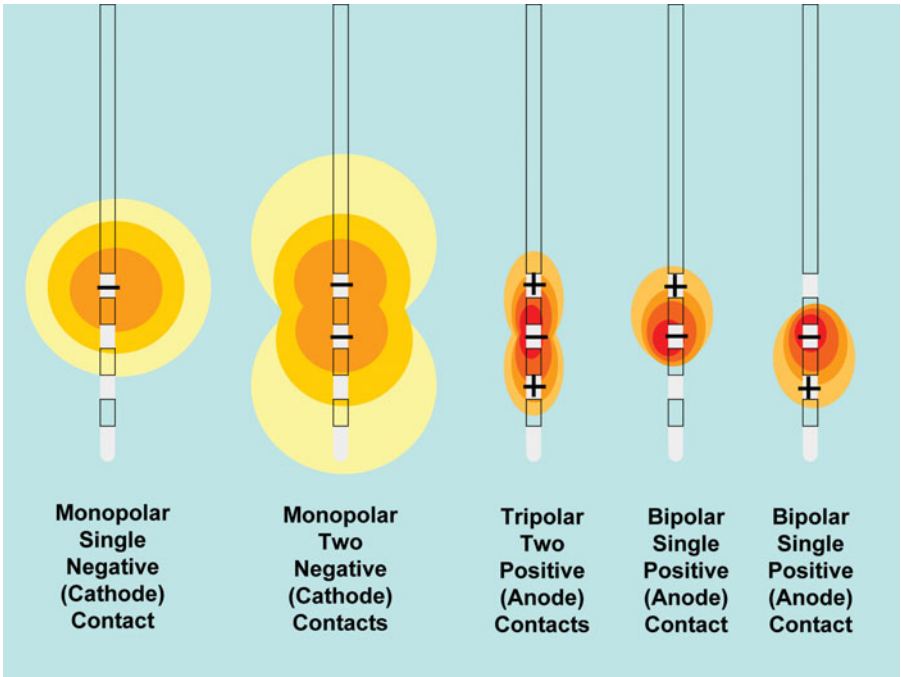

FIGURE 3.22. *The variety of electrical fields that can be created by multiple active contacts. Some situations may require unusual electrode configurations. For example, where greater therapeutic efficacy is needed, multiple active negative contacts can be used to generate larger electrical fields as long as the electrical current does not spread to structures in which axon activation is undesirable. The tripolar configuration can greatly restrict the horizontal spread of the electrical field to prevent side effects.*

It is not clear that the phase delay between the DBS pulses of each group are such that the effects of the two groups are synergistic, resulting in an effective field (see Figure 3.23D), or whether the effects are just those associated with each group (see Figures 3.23B and 3.23C). Hypothetically, neither of the electrical fields generated independently by each set of electrode configurations and stimulus parameters are effective, and if the interleaved stimulation by both sets is not synergistic, then there may not be any value in combining them. Although the time of the phase delay is likely to be quite small (depending on the DBS frequency, with the delay between the two interleaved pulses equal to one-half of the time between two successive pulses of one group; see Figure 3.23), it is unclear whether it is short enough to allow a synergistic effect. For example, DBS at 100 pps may not be effective, whereas DBS at 130 pps may be. Thus, the time difference in the interstimulus interval between the 100- and 130-pps DBS is approximately 2.3 ms, and this is enough to make a therapeutic difference. Interleaved stimulation at 100 pps results in a time delay between each pulse of the two groups of 5 ms which could affect any possible synergy between the two groups in the interleaved stimulation.

There is also the concern that the electrical fields generated by each group could overlap. This could cause a potentially dangerous additive charge density, particularly at long pulse widths. Consequently, the manufacturer may limit the frequency to 125 pps. The rationale for limiting the maximum frequency in the interleaved mode to

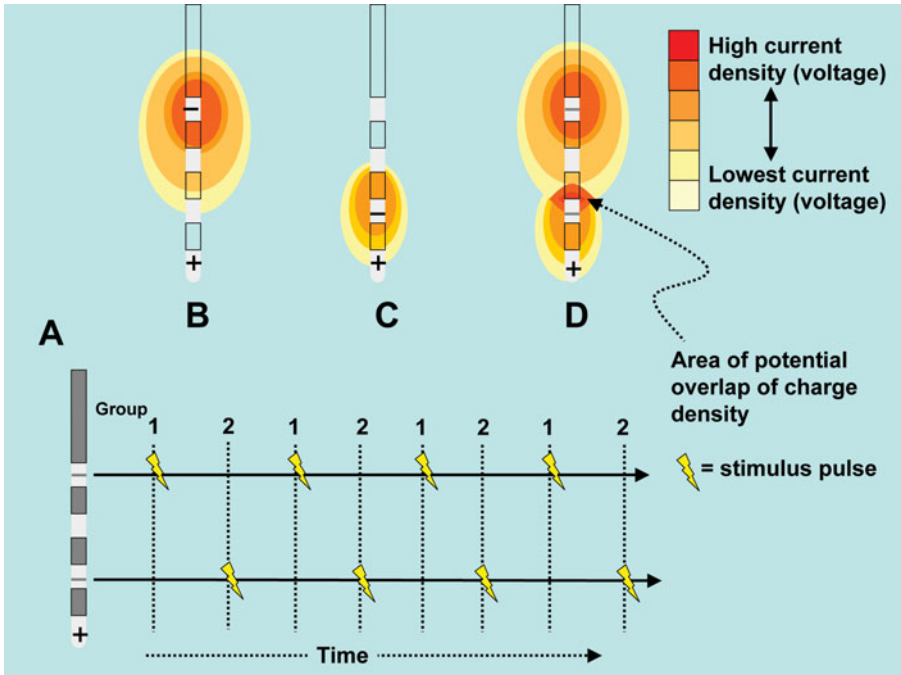

FIGURE 3.23. *Effects of two stimulation groups (combinations of electrode configurations and stimulation parameters). Two commercially available IPGs provide for nearly simultaneous delivery to two stimulus trains (called groups). The two trains have the same frequency but are offset (phase delay) so that the stimulus pulse in one group follows the stimulus pulse of the second group (A). The two groups can vary in current/voltage, pulse width, and polarity but not frequency (rate). Thus, each group can be associated with a different electrical field (B and C). Theoretically, the two groups could give an effective electrical field that is some combination of the two (D). However, it is not clear whether the phase delay is such that the effects of the two groups are synergistic, resulting in an effective field as in D, or whether the effects are just those associated with each group (B and C). Note that for commercially available IPGs capable of interleaved DBS, the phase delay between the pulse of group 1 and the subsequent pulse in group 2 is one-half of the time between successive group 1 pulses (A). This means that the phase delays are dependent on the DBS frequency. There is a concern that the electrical fields generated by each group could overlap, causing a potentially dangerous additive charge density, particularly at long pulse widths. Consequently, the manufacturer of the commercially available device limits the frequency to 125 Hz.*

125 pps is unclear, particularly as clinical studies demonstrate many patients requiring higher DBS frequencies (rates). Furthermore, neurons in the overlapping area could theoretically be subject to DBS at twice the frequency (rate) as neurons in the nonoverlapping area. There is insufficient evidence regarding the potential additive effect of the two different groups, so it is unknown whether the effects would be any different than for either group given alone and what advantages this would have clinically.

The previous discussion evidences the value of being able to sculpt the electrical field, and in large part this ability is related to the physical structure of the electrodes and the ability to deliver varying electrical currents to the electrodes. Commercially available DBS leads use a linear array of electrodes that wrap around the full circumference of the lead shaft. Although having these electrodes at different lengths along the long axis of the lead allows one to move the electrical field up and down the shaft of the lead, this arrangement does not allow directing the electrical field in a restricted direction in the plane orthogonal to the long axis of the DBS electrode array.

In other words, controlling the electrical field in front or back of, or medial or lateral to, the DBS lead is problematic. A segmented electrode that was only a part of the circumference would allow for better directional specificity (see Commentary 3.3).

The stimulation parameters of an ideal DBS system would allow for constant-*current* stimulation in a large variety of electrode configurations. Furthermore, the constant current could be parsed among different contacts simultaneously rather than interleaved. Capitalizing on biophysical properties, the waveforms of the stimuli could be controlled. For example, a long subthreshold depolarizing current would inactivate the Na^+ conductance channels in axons close to the electrode but not in axons further away, thereby allowing selectivity. A subsequent suprathreshold depolarizing current would activate axons at some distance to the DBS electrode. This

Commentary 3.3 ***The Ideal DBS System***

The proliferation of DBS systems allows for customization to meet the unique needs of the individual patient. However, the multiplicity of different systems, both current and anticipated, increases the complexity of deciding which to use. This book does not make any direct comparisons or recommendations because it is anticipated that new devices will become commercially available, possibly with features that cannot be anticipated. Consequently, the ideal DBS system is described to act as a benchmark for future comparisons.

The ideal DBS system should provide constant-*current* stimulation. The advantages of a consistent clinical response in the face of changing impedances and the more effective stimulation pulse waveforms have been discussed previously (see Figures 2.2 and 2.4). Furthermore, even in those patients whose impedances stabilize some period of time after DBS lead implantation, different contacts on the same DBS lead can have widely varying impedances. This makes generalization of experience based on the constant-*voltage* stimulation problematic because effects or side effects on one electrode contact often do not generalize to a different contact on the same DBS lead in the same patient because of the possibility of different impedances.

The DBS system should allow for a precise sculpting of the electrical field and the ability to move the field in any direction. One approach would be to allow parsing of different currents onto cathodes and anodes (see Figure 3.23). Furthermore, the DBS pulses for each of the different cathode and anode currents should be "physiologically" at the same time. This means that when two or more cathodes of different electrical currents are active, the effects are synergistic. It is not clear whether the interleaving of different pulses on different contacts on the same lead acts synergistically to produce a greater physiological effect than each of the pulses on each contact (see Figure 3.23).

Current systems use a linear array of contacts (typically four) arranged as cylinders in which the electrical contact spans the entire circumference. Although the linear array of contacts allow for moving the electrical field up and down the long axis of the lead, they do not allow restriction of the electrical field in the plane orthogonal to the long axis of the lead (Figure 3.24). The ideal DBS lead would have segmented electrical contacts that would allow control of the electrical field in the plane orthogonal to the long axis of the DBS lead (see Figure 3.24).

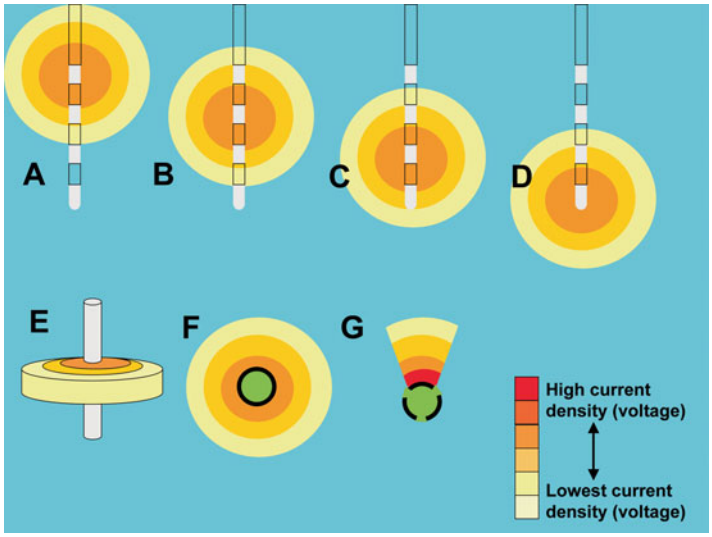

FIGURE 3.24. *The arrangement of electrical contacts on commercially available IPGs consists of a linear array of contacts. The distribution of the electrical field associated with DBS can be moved up and down the long axis of the DBS lead (A–D). However, the distribution in the plane orthogonal to the long axis of the DBS lead cannot be controlled (E). This is because the electrode contact surface extends completely around the circumference of the contact, sending out electrical charge in all directions (F). In the future, segmented electrode contacts may allow projecting the electrical field in one direction in the plane orthogonal to the long axis of the DBS lead by stimulating through only one segment (G). Thus, if a DBS lead is too lateral in the STN causing tonic muscle contraction by spread to the corticospinal tract in the internal capsule, only the medial-facing segment could be stimulated, thereby projecting the electrical field medially away from the corticospinal tract.*

would have the effect of "projecting" the activating electrical field out and away from the DBS electrode. Finally, the ideal system would provide for complex stimulation patterns to optimize the physiological effects—for example, interleaving different DBS frequencies simultaneously or using random DBS spike trains of varying bandwidth to take advantage of biophysical phenomena such as stochastic resonance and stochastic coherence.

This book assumes a DBS lead that is a linear array of four electrical contacts, as represented in the figures. This is based on the currently commercially available DBS system and also systems currently under clinical trials but not yet approved by the Food and Drug Administration (FDA). However, the principles outlined in this book are applicable to any type of DBS lead. Note that there currently are two commercially available DBS leads, not to be confused with the four IPGs, that differ in their spacing between electrical contacts. You should consult the manufacturer's information regarding the construction of the DBS leads you are using.

Monopolar and bipolar configurations are most commonly used. However, in other circumstances, multiple negative contacts or tripolar configurations are needed because of their unique shapes and spatial orientations (see Figure 3.22). The principles determining the shape, size, orientation, and intensities for these configurations follow the same principles as described previously for monopolar and bipolar

configurations. For example, for tripolar configurations, the intensity of the electrical field falls off as the cube (power of 3) of the distance from the negative contact, as described here:

$$\text{Electrical charge} \propto d^2/r^3 \tag{3.3}$$

Multiple active contacts greatly increase the current drained from the IPG battery, thereby shortening its life and necessitating more frequent replacement. In the case of rechargeable IPGs, the greater current drain increases the risk of IPG failure if the IPG is not recharged frequently enough. Also, multiple active electrode configurations pose substantial safety concerns when using constant-*voltage* (not constant-*current*) IPGs. Electrical charges administered to the brain may change substantially when impedance changes, as occurs when changing electrode configurations, if there is not a corresponding change in the voltage (see Figures 2.2C and 2.2D). Check the impedance according to the manufacturer's recommendations when changing electrode configurations before increasing the voltage, pulse width, or frequency, to avoid dangerous electrical charges in the brain when the impedance changes. Various IPGs may have several methods for checking impedances. Be sure the method you use for the purpose described previously uses the same settings and electrode configurations that you intend to use therapeutically.

The critical issue is the charge density, which is the amount of electrical charge (measured in microcoulombs) per surface area (cm^2) per each phase of the DBS pulse. The currently accepted safety limit is 30 $\mu C/cm^2$/phase. Increasing the number of active contacts decreases impedance, resulting in a greater flow of electrical current for a constant voltage, as in the case of constant-*voltage* IPGs, as well as increasing the surface area of the electrical contacts. However, these changes may not offset each other, particularly because the relationship of electrical current to voltage and impedance is nonlinear. Consequently, a doubling of the surface area with a halving of the impedance does not necessarily result in the same electrical current density. Constant-*current* IPGs automatically adjust the voltage with changes in impedances to maintain the same electrical current, thereby avoiding this complication.

In commercially avialable IPGs, two types of impedances can be measured: electrode impedance and therapeutic impedance. Electrode impedance is the resistance to the flow of electrical charge with each monopolar and bipolar configuration. The current/voltage, pulse width, and frequencies used to determine electrode impedances are generally not the same as those used in therapeutic DBS. Electrode impedances are not relevant for safety concerns; rather, they are used primarily to check the electrical integrity of the DBS system. Therapeutic impedance is the resistance to electrical flow for those stimulation parameters and electrode configurations that are currently in use to treat the patient. Therapeutic impedance is particularly relevant to safe use of DBS. The charge density that a patient is exposed to with stimulation is related to the therapeutic impedance and not the electrode impedance unless the electrode impedance is checked using the same electrode configuration and parameter settings as are used therapeutically.

There have been concerns about the accuracy of the therapeutic impedance measurements in currently commercially available IPGs. The issue may relate to whether the voltage used in the therapeutic impedance test is sufficient. Be sure to

consult the manufacturer's information. For example, with currently available IPGs, a patient may have a very high therapeutic impedance, suggesting a break in the conductor, but a check of the electrode impedance could show that it is within normal operational limits. This is most likely to occur with a low stimulation voltage. A useful test in this situation is to increase the stimulation voltage and recheck the therapeutic impedance.

Most IPGs warn when the safety limit is approached. However, some IPGs employ certain assumptions that may not be valid in a particular patient. If the assumed impedances are greater than the actual impedance, the IPGs may underestimate the charge density, risking excessive injection of electrical charge into the brain. If the estimated impedances are less than the actual impedances, then the IPG may give a false warning and this could discourage, inappropriately, the use of higher stimulation strengths. You should be thoroughly familiar with the issues of impedance checking in the IPGs you use.

The ideal DBS system would allow leveraging various biophysical properties to achieve unique effects, such as the ability to project the effective electrical field away from the electrode contact surface. For example, prolonged subthreshold depolarization results in inactivation of Na^+ conductance channels, thereby preventing the generation of action potentials. This phenomenon could be exploited by inactivating axons relatively close to the electrode surface while axons farther away are still sensitive to the DBS activation (Figure 3.25).

Other types of DBS pulse waveforms may selectively activate cell bodies or axons, which could allow better efficacy and fewer side effects in situations in which either the cell bodies or the axons selectively cause either efficacy or side effects. Another property that could allow more selective activation of neurons is based on chronaxie, which, roughly, is the amount of electrical charge that is related to the duration of the

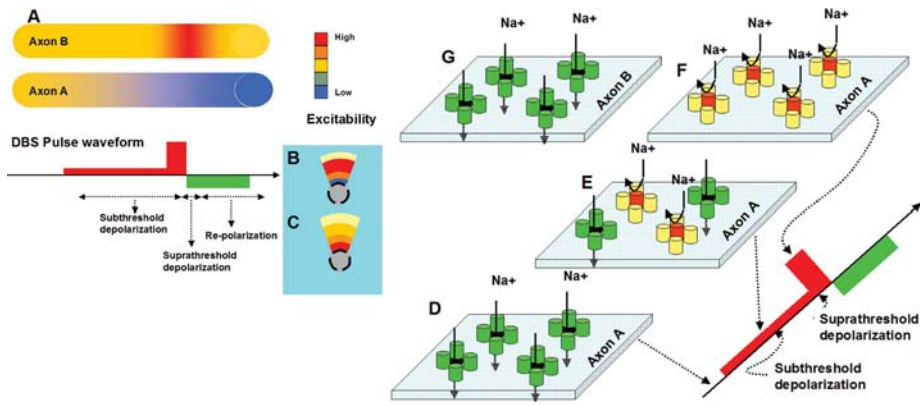

FIGURE 3.25. *Example of leveraging biophysical properties to affect the shape and distribution of the DBS electric field. Effects of an initial subthreshold depolarization phase in the DBS pulse waveform allow reduction in the excitability of axons nearer the electrode contact while maintaining excitability of axons farther from the electrode contact (A). With only a suprathreshold depolarization, the highest activation is of axons near the electrode contact surface (C). The subthreshold prepulse allows the excitability to be "thrown" farther away from the contact surface (B). Initially, the Na^+ conduction channels are active (capable of being opened) in both axons A and B (D). The low-voltage subthreshold depolarization causes an inactivation of the Na^+ conductance channels but only in axon A (E). By the time the suprathreshold depolarization phase occurs, all the Na^+ conductance channels in axon A are inactivated (F) and axon A cannot generate an action potential. The Na^+ conductance channels in axon B are active (G) and can generate an action potential in response to the suprathreshold phase of the DBS pulse.*

stimulation cathode phase, and is necessary to cause an action potential. Axons are excited at short pulse widths, whereas cell bodies or dendrites are not.

Another biophysical property that can be exploited is the refractory period, which differs among axons, cell bodies, and dendrites. If a pair of stimulation pulses is administered at an interpulse interval shorter than the refractory period, then the second of the pair of pulses will occur with the neuronal element in its refractory period; consequently, the [OR] period and, consequently, the neuronal element will not respond to the second pulse. The refractory period of a cell body or dendrite, such as 2 ms, is longer than that of an axon, typically less than 1 ms. Thus, whereas pair of stimulation pulses with an interstimulus interval of 1 ms has the effect of only one pulse for the cell body or dendrite, the pair of stimulation pulses will have the effect of two pulses on the axon.

The ideal IPG would allow for an arbitrarily wide range of stimulation patterns, from paired pulses as described previously to "noisy" patterns with frequencies over specific bandwidths. "Noisy" stimulation could improve the signal-to-noise ratio caused by disease that corrupts information processing within the brain causing misinformation. Although counterintuitive, adding noise to a poor signal-to-noise condition can actually improve the signal through a process called stochastic resonance.

The Systems Oscillators theory posits that different reentrant neural oscillators within the same basal ganglia-thalamic-cortical network operate over different frequency bands (see Chapter 12) (Montgomery, 2008b). For example, the dysynaptic oscillator, the thalamocortical circuit, operates at approximately 147 Hz. DBS at this frequency can resonant amplify the signal in this frequency range just as the oscillator in an AM radio amplifies (i.e., selects) the appropriate radio signal from the radio station. Different oscillators within the basal ganglia–thalamic–cortical system may require stimulation at different frequencies to resonant amplify the information carried within those specific oscillators. For example, the ability to recruit motor units may require high-frequency DBS to resonant amplify the thalamic–motor cortical system in order to increase muscular effort. However, the precise modulation of motor unit activity over the longer time course of a behavior may require DBS at lower frequencies. This may explain why low-frequency DBS may be more helpful for gait and speech (see Chapter 12). The ideal IPG would provide for DBS trains that could supply stimulation at multiple frequencies in an interleaved or multiplexed manner.

If neural systems physiology and pathophysiology research and research into the therapeutic mechanisms of action are supported and expanded, then the potential applications of brain stimulation will increase. This could provide help to the countless patients who are not adequately responding to pharmacological therapies, including stem cell and gene therapies. Advances in neural systems physiology and pathophysiology and in the therapeutic mechanisms of DBS could be translated into new engineering solutions that will become the basis for the ideal IPG of the future.

A number of practical issues may be improved by future ideal IPGs. Therapeutic impedances and warnings could be more straightforward. Device- and patient-specific information allowing efficient use with respect to prolonging battery and recharge use would be appreciated. Rechargeable IPGs could reduce repeated surgical trauma associated with battery replacement and reduce cost. However, the ideal IPG

Table 3.1. ***A Report Card for Noting the Various Features of Specific IPGs***[a]

IPG model name: _____ Manufacturer: _____

_____ Single channel _____ Dual channel

Stimulation mode

_____ Constant-current, _____ constant-voltage

_____ Both constant-current and constant-voltage

_____ Capable of true partitioning of stimulation current among contacts on a single DBS lead, _____ not capable

_____ Capable of multiple interleaved stimulation, _____ not capable

Stimulation pulse train

_____ Single regular frequency per IPG

_____ Multiple regular frequencies per IPG _____

_____ Wide range of DBS stimulation patterns programmer defined

For constant-*current* stimulation

Minimum frequency _____ Maximum frequency _____

For constant-*voltage* stimulation

Minimum frequency _____ Maximum frequency _____

Electrode configuration

_____ Multicathode/multianode capable in constant-current mode, _____ not capable

_____ Multicathode/multianode capable in constant-voltage mode, _____ not capable

_____ Segmented contacts, _____ single circumferential contacts

Battery voltage _____

_____ Rechargeable, _____ not rechargeable

Efficiency loss with stimulation exceeding battery voltage[b]

_____ Inefficient _____ moderately efficient _____ very efficient

Simulation charge density safety alert

First-order warning

_____ Based on assumed impedances, _____ based on measured impedances

Second-order warning

_____ Based on assumed impedances, _____ based on measured impedances

Electrode impedances

Impedance suggestive of circuit break >_____

Current suggestive of circuit break <_____

Impedance suggestive of short-circuit <_____

Current suggestive of short-circuit break >_____

Patient/caregiver controllable

_____ Not capable, _____ single parameter programmer defined

_____ Multiple parameter programmer defined

_____ No feedback to patient/caregiver, _____ clear feedback

_____ Able to switch between programmer-defined configurations/parameters

[a] See also Commentary 3.3.

[b] At the time of publication, there was insufficient information to make independent judgments. However, information similar to that described in Figure 6.1 may help in estimating efficiency.

would not allow a patient or caregiver to let the battery charge to run out. Although external reminders would be helpful, they could easily be forgotten or ignored. An adequate warning device incorporated into the IPG, such as a vibration, would be difficult to ignore. Alternatively, the time course of IPG failure due to lack of recharge should be gradual so as to allow a gradual deterioration of the patient's symptoms, thereby reminding the patient and/or caregiver without endangering the patient. There have been case reports of serious sequelae of sudden device failure in patients with Parkinson's disease due to sudden device failure.

Miniaturization of the IPGs so that they could be placed in the head rather than in the chest would obviate the need for tunneling the extension wires and increase patient comfort. DBS systems that are not affected by the external electrical environment would uncomplicate patients' lives and medical care.

Given the increasing number of commercially available and anticipated DBS systems, particularly IPGs, it is difficult to provide information specific to each IPG that does not risk obsolescence. Furthermore, comments about anticipated but not yet FDA-approved IPGs would be to invite perhaps untoward interest by the FDA, potentially reflected on the manufacture. Consequently, a report card is presented in Table 3.1 that can be copied and used to collect information regarding DBS systems used. This can be kept available for ready reference.

4 DBS Safety

Excessive electrical charges can damage tissue. The safety limit typically is defined as the *charge density*, which is the amount of electrical charge delivered divided by the surface area of the electrical contact. The generally accepted safety limit is 30 $\mu C/cm^2$/phase. Microcoulombs is the number of units of electrical charge administered into the brain (μC), and square centimeters (cm^2) is the surface area of the active electrical contacts. Phase refers to the negative (cathodal) and positive (anodal) phase of an individual DBS pulse (Figure 4.1). The phase is the part of the DBS pulse associated with one polarity of electrical current. The negative (cathodal) phase is associated with negative electrical charges flowing from the electrical contact. A positive (anodal) phase is associated with negative electrical charges flowing into the contact (sometimes referred to as anodal current). The negative (cathodal) and positive (anodal) phases of the individual DBS pulse should not be confused with the negative (cathode) and positive (anode) electrical contacts. The difference in the neurophysiological (and hence clinical) effect between the negative and positive contacts is that the height of the negative (cathodal) current at the negative contact in the first phase is sufficient to activate axons, whereas that during the second (anodal) phase at the positive contact is not.

The electrical charge density is the total charge per pulse divided by the surface area of the active DBS contact. The total charge is the current times the pulse width. The current is the voltage divided by the impedance. Thus, a 10-V DBS pulse through a contact with 1000 Ω of impedance for a pulse width of 90 μs delivered through a DBS contact that is 1.5 mm (0.15 cm) in length and 1.2 mm (0.12 cm) in diameter results in a charge density of approximately 1.14 $\mu C/cm^2$/phase, where the phase is the pulse width in seconds.

For commercially available IPGs, the two phases of the DBS pulse differ in the height and duration of electrical current/voltage (see Figure 4.1). Programmers should consult the manufacturer regarding the specific IPG used. In some IPGs, the initial phase is higher, meaning that a greater intensity of electrical current/voltage is applied but for a briefer period than in the second phase. However, the area under the curve for each phase of the individual DBS pulse is the same. This equality means that the total amount of charge administered during the first phase by the negative (cathodal) current is taken back in by the second positive (anodal) phase. An imbalance in the area under the curve, representing a surplus of electrical charge on the neural membrane, can damage brain tissue. Some IPGs are capable of cycling mode stimulation, where the DBS stimulation train is turned on for a defined period of time and then turned off for a defined period of time. For some IPGs, cycling mode stimulation could cause a charge imbalance that could be sufficient to cause brain injury. You should check with the manufacturer regarding cycling mode stimulation.

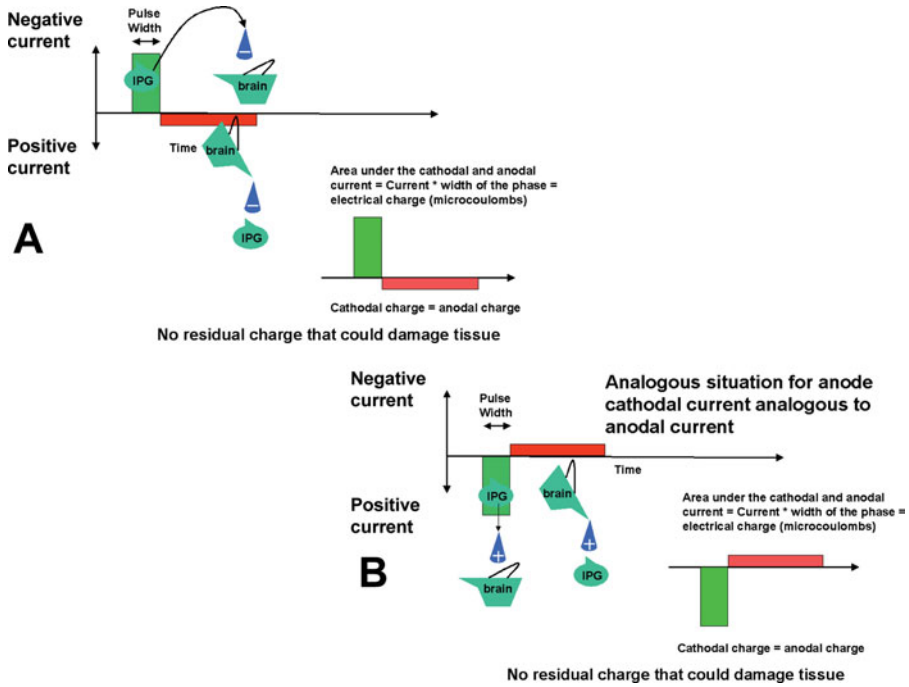

FIGURE 4.1. *Waveforms of individual DBS pulses illustrating the distinction between a negative (cathode) contact and negative (*cathodal*) current or phase and the similar distinction between a positive contact and positive (*anodal*) current or phases of electrical current administered into the brain with each DBS pulse. The distinction is important. Note that both contacts that are designated the cathode (negative) and anode (positive) contacts pass both negative (negative charges coming out of the contact or cathodal current) and positive electrical current (actually negative charges going into the contact or anodal current). The naming convention of the contacts is based on the initial phase or component of the stimulus waveform. (A) The situation for a cathode (negative) contact in which negative current is going from the IPG into the brain during the first phase. During the second phase, negative current is going from the brain back into the IPG (referred to as positive or anodal current). Alternatively, considered from the standpoint of the brain, this is a positive current going into the brain during the second phase counterbalancing the negative current during the initial or first phase of the DBS pulse. (B) The configuration in which the contact is an anode (positive) contact because the first phase of the DBS pulse can be considered a relatively positive current (negative charges going from the brain into the contact). The second phase would be a negative current. Note that with the circumstance of B with available commercial IPGs, this arrangement requires a bipolar configuration because the IPG cannot act as a cathode (negative) contact nor can it act as an anode (positive) contact if one of the DBS lead contacts acts as an anode (positive) contact. Also note that the area under each phase is the same. The initial phase, either cathodal (negative) or anodal (positive) contacts, has a higher electrical current but a briefer duration than the following phase with reversed current. However, the same amount of electrical charge administered during the first phase is returned during the second phase.*

Tissue can be damaged through *electrolysis*, in which water molecules are broken down into hydrogen and oxygen gas bubbles. Fortunately, this process is reversible so that when the current reverses between the first and second phases of each DBS pulse, the hydrogen and oxygen bubbles recombine to form water. However, if bubbles accumulate, they can tear and damage tissue. Residual electrical charges resulting from charge imbalances as described previously can result in marked bubble formation and possibly tissue damage.

Another way in which DBS can damage the brain is by the heat generated when electrical current is passed through the brain. Passing electrical current through a conductor with resistance (or impedance in the case of DBS) generates heat. The more electrical current that passes through the impedance of brain tissue, the higher

the risk of overheating and tissue damage. Factors related to the risk of heat damage include increases in current/voltage, pulse width, and the rate at which pulses are delivered (DBS frequency).

The safety of electrical stimulation is directly related to the electrical current density, which is determined by the amount of administered electrical charge and the surface area of the cathode. For the same voltage, as provided by constant-*voltage* IPGs, multiple cathodes reduce impedance, increasing the current that is administered into the tissue. Counterbalancing the decrease in the impedance is the greater surface area offered by multiple cathodes, which decreases current density. However, this decrease is nonlinear so that halving the impedance does not counterbalance doubling the surface area. Also, all contacts and the IPG case can act as either cathodes or anodes. Thus, a contact designated as the anode in one electrode configuration during programming becomes a cathode during the second DBS phase.

When the IPG case is the anode in the electrode configuration, its large surface area is likely to more than compensate for any reduction in therapeutic impedance. However, the same is not true for the DBS lead anode in bipolar electrode configurations. The larger electrical charge administered from multiple cathodes during the first phase becomes the cathodal current administered into the brain through the anode during the second phase. If there are fewer designated anodes than cathodes, the current densities at the designated anodes can be higher than anticipated. For example, consider the electrode configuration in which there are two cathodes (negative contacts) and a single anode (positive contact) that are on the DBS lead rather than the IPG case. During the first and second phases of the DBS pulse, current will be flowing out of and then into two cathodes. The electrical charge delivered at the two cathodes (negative contacts) will be diluted by the doubling of the surface area because two contacts are used. However, that same amount of current that flows out of and then into the two cathodes (negative contacts) must flow into and then out of the single contact, and the charge density at the anode (positive contact) will be twice that at the two cathodes (negative contacts). This could be a serious problem if the use of multiple cathodes (negative contacts) significantly reduces the impedance. In the situation in which the IPG case is used as the anode (positive contact), the large surface area would greatly reduce the charge densities.

Many IPGs may have built-in safety warnings. Some commercially available IPGs make assumptions about the impedance of the electrode configurations when calculating the electrical current to be administered into the brain. Some IPGs assume that the impedance is 500 Ω. If the actual impedance is less than 500 Ω, harmful stimulation may occur before the warning is given. If the impedance is substantially higher than 500 Ω, the warning may be expected but false, and you may decide not to use parameters that would benefit the patient. You should review the appropriate manufacturer manuals for the IPG you are using.

Some IPGs allow the patient or caregiver to change certain DBS stimulation variables, such as voltage. However, these IPGs may not warn the patient or caregiver if the safe stimulation level is exceeded when the patient or caregiver modifies the stimulation parameters. Usually, the professional programming device will provide a warning when the limits of the allowable patient or caregiver controllable parameters

are programmed. However, this may be based on assumed impedances that may or may not be accurate (as discussed previously). Consequently, you should always determine the upper limit of the stimulation variable that the patient can use safely and restrict the ability of the patient to exceed that limit. Review the appropriate operation and safety manuals of the systems you use, and when in doubt, consult the manufacturer.

Potential Psychosocial Consequences of DBS

After years of disability and dependence, patients experiencing the often dramatic and relatively rapid improvements in their neurological disabilities may become distressed (Schüpbach et al., 2006). Such distress is related not only to the mood changes that can accompany successful DBS treatment but also to their effect on the personal relationships between patient and family. The psychological and sociological adaptations to the patient's disease may suddenly become maladaptive when the patient has greater function and perhaps independence. In my experience, this phenomenon is not unique to patients with neurological disorders who have been treated with DBS. It also occurs in patients treated with levodopa and, indeed, in many instances in which chronic dependence is suddenly relieved by effective therapy.

These psychosocial stresses are difficult to predict but, fortunately, are not frequent. However, they can be catastrophic, so you need to anticipate them and monitor the patient closely. Often, establishing a rapport and familiarity with the patient and caregivers through frequent and unhurried contact over time can help you detect these stresses early.

5 The Issue of DBS Frequency

Thus far, the electrophysiological effects of DBS frequency have been discussed only briefly. Old notions incorrectly held that high-frequency DBS inhibited neuronal elements in the stimulated tissue, whereas low-frequency DBS excited them. This notion was based on clinical observations of DBS in patients with Parkinson's disease or essential tremor. High-frequency DBS improved symptoms and low-frequency DBS often worsened them. Also, the similarity in the clinical effects of high-frequency DBS and surgical ablation was thought to indicate a similar mechanism of action, which is not correct. Finally, because both pallidotomy and high-frequency globus pallidus internal segment (GPi) DBS relieved the symptoms of Parkinson's disease, the mechanisms of action were again erroneously thought to be the same. An analogous error would be to infer the same mechanism in the circumstance in which both a stroke in the motor cortex and curare produce paralysis.

Another reason for misunderstanding the mechanisms of DBS action is that the inhibition of the GPi or subthalamic nucleus (STN) in patients with Parkinson's disease by high-frequency DBS is consistent with current notions that overactivity of the GPi and STN causes the symptoms and disabilities of this disease. Considerable evidence has been gathered during the past 20 years indicating that overactivity of the GPi or STN is not causally related to Parkinson's disease (Montgomery, 2007a). For example, resting or baseline neuronal activity in the STN of patients with Parkinson's disease is no different from resting or baseline STN neuronal activity in patients with epilepsy (Montgomery, 2008c). (An interesting aside: When asked why they continue to teach this outmoded notion that overactivity of the GPi causes the disabilities of Parkinson's disease, educators typically respond that this information is expected on board examinations. When those preparing the questions for board examinations are asked why this notion is the expected answer, they respond that this information is what is being taught in medical school.)

Low-frequency DBS was and sometimes still is thought to excite neurons in the target. However, evidence from DBS-related research in nonhuman primates shows that the *qualitative* changes in neuronal responses to high-frequency DBS of the STN are the same as the responses to low-frequency DBS. However, there are *quantitative* differences in the responses to low- and high-frequency DBS and, in the case of STN DBS, the magnitude of these responses is greater with high- than with low-frequency DBS (Montgomery and Gale, 2008).

In the past, nearly all therapeutic DBS was high-frequency stimulation. It is now clear that in some circumstances, low-frequency DBS is more effective. Low-frequency DBS of the GPi may help dystonia when high frequencies do not (Alterman et al., 2007). Indeed, in some circumstances, high-frequency DBS of the

STN may worsen symptoms. For example, high-frequency DBS can worsen speech, whereas low-frequency DBS may improve it (Montgomery, 2007b). Similarly, high-frequency DBS of the STN may worsen gait, whereas low-frequency DBS may improve it (Moreau et al., 2008) (see Commentary 5.1).

Commentary 5.1. ***Emergence of Therapeutic Low-Frequency DBS***

Conventional wisdom is that high-frequency DBS helps and that low-frequency DBS worsens neurological symptoms. However, this wisdom is no longer true, at least for some disorders, such as Parkinson's disease and dystonia. High-frequency STN stimulation can worsen speech (Montgomery, 2007b) and gait, whereas low-frequency may improve them (Moreau et al., 2008). Similarly, DBS of the pedunculopontine nucleus for gait and balance problems in patients with Parkinson's disease is most effective at low frequencies (Mazzone et al., 2005). Low-frequency DBS may help in some cases of dystonia when high-frequency DBS is not completely effective (Alterman et al., 2007). In these cases, the programming algorithms for the typical high-frequency DBS described in this book can be applied by substituting "low-frequency" for "high-frequency" DBS and substituting 40 pps for 130 pps, or even 20 pps for 130 pps (see Figures 6.3 and 6.4 and also Figures A3.2 and A3.3). Note that some IPGs allow different DBS frequency (rate) ranges depending on whether the IPG is in constant-*voltage* or constant-*current* mode or in interleaved mode. For example, if the lowest frequency in the constant-*current* mode is 30 pps, then patients requiring lower frequencies, as may be the case for speech or gait problems, may not be able to use the constant-*current* mode, with the loss of advantages that constant-*current* stimulation provides.

The therapeutic efficacy of DBS, particularly for speech and gait, belies a current theory of basal ganglia physiology and pathophysiology. This theory suggests that a 20-Hz oscillation within the basal ganglia causes the slowness of movement (bradykinesia) or absence of movement (akinesia) and, consequently, the 20-Hz oscillations are termed *antikinetic*. In contrast, the presence of a 70-Hz oscillation with effective treatment suggests that the 70-Hz oscillator promotes movement; hence the term *prokinetic* (Hutchison et al., 2004). Thus, according to this theory, high-frequency DBS is effective in Parkinson's disease because it suppresses the 20-Hz oscillation and supports the 70-Hz oscillation. Certainly, DBS at 20 pps can worsen motor control of the limbs. However, DBS at 20 pps improves speech and swallowing.

There are at least two logical explanations for this contradiction. First, different functions—that is, upper extremity functions versus lower extremity functions—have different anti- and prokinetic oscillators at different frequencies. For example, the 20-Hz oscillations may be anti-kinetic for upper extremity functions and pro-kinetic for lower extremity functions. The 70-Hz oscillator (actually higher frequencies) may be pro-kinetic for upper extremity function and anti-kinetic for lower extremity function. The more likely case is that the 20- and 70-Hz oscillations are epiphenomenal. Interestingly, DBS at

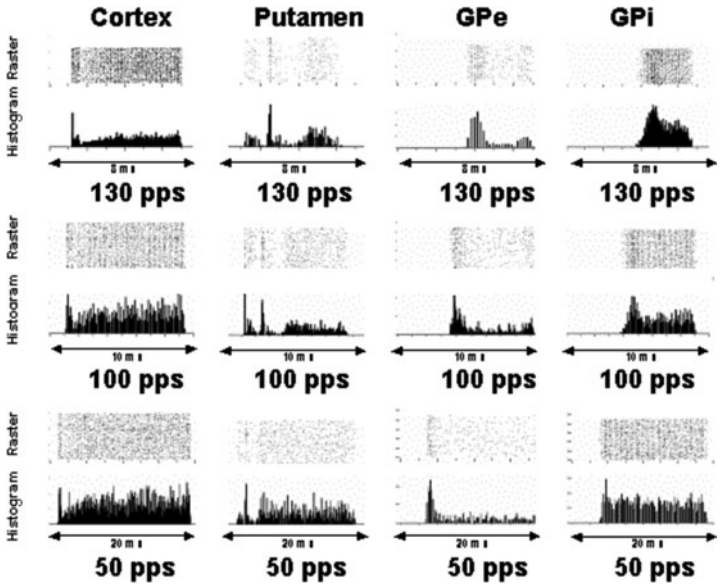

FIGURE 5.1. *Rasters and histograms for representative neuronal responses of the motor cortex, GPi, globus pallidus external segment (GPe), and putamen to STN DBS at different frequencies. Each structure and frequency of DBS is represented by two figures. The top figures are post-stimulus rasters, which show the discharge of the neurons in the interval between each DBS pulse, which occurs at time 0. Each row in the raster represents the neuronal response to the DBS pulse, and each dot represents the discharge of the neuron. The responses in the rasters are then organized and summed in columns for increments of time to construct the histograms (the bottom figure of each pair), which show the average response over time after the DBS pulse. The length of each raster and histogram represents the time between DBS pulses. As can be seen, for each neuron in the different structures, the immediate responses to the DBS pulse are not qualitatively different at the different DBS frequencies. However, the relative magnitude of the effects differs with DBS frequency such that for many neurons, the magnitude of the response is highest for the 130-pps DBS (not shown). (Reprinted from Montgomery and Gale, 2008.)*

70 pps appears to have little therapeutic effect, which is not what would be expected if the 70-Hz oscillations in the basal ganglia were prokinetic.

Also intriguing are observations in nonhuman primates that STN neuronal responses to high, moderate, and low DBS frequencies are qualitatively similar (Montgomery and Gale, 2008) (Figure 5.1). Regardless of the DBS frequency, there is a series of activations followed by reductions (probably related to refractory periods). However, the quantitative response is greater with high-frequency DBS than it is with moderate- and low-frequency DBS. The magnitudes of the responses are different depending on the frequency of DBS, particularly those occurring at approximately 4 ms after the DBS pulse. This means that the response to one DBS pulse is influenced by the presence of preceding pulses—but not just any preceding pulse. In these experiments, for the 130-pps DBS, a pulse was given approximately 7 ms before the pulse used to start the peri-event raster and histogram (see Figure 5.1) rather than 10 or 20 ms before the index pulse of the 100- and 50-pps DBS. Thus, the probability of a neuronal response to the DBS pulse was increased only when the preceding DBS pulse occurred approximately 7 ms before the index pulse.

(*continued*)

Commentary 5.1 (*continued*)

The Systems Oscillators theory offers an explanation of DBS frequency effects (Montgomery, 2004a, 2007a,b, 2008b). This theory posits that the basal ganglia–thalamic–cortical system is a network of embedded or nested oscillators representing many different frequencies. DBS resonates with specific oscillators within a system in a manner analogous to AM radio transmissions. The radio station broadcasts a carrier frequency that transmits information encoded in the varying amplitudes of the carrier frequency. A receiving radio has an oscillator that generates an electronic frequency. When the receiving radio's oscillator is tuned to resonate with the amplitude-modulated carrier frequency from the radio station, the signal is amplified above all the other signals received by the radio's antenna (see Chapters 12 and 14). Otherwise, the desired signal is lost in the noise of countless other radio signals.

The Systems Oscillators theory also proposes that different functions have different carrier frequencies. These frequencies are determined in large part by the underlying anatomy. Longer loops, for example, that might involve the brainstem for gait and perhaps speech, operate at lower frequencies than shorter loops, such as those involving upper limb control, that operate at high frequencies through the corticothalamic oscillator (Montgomery, 2007b).

It is unclear how the frequency of DBS relates to improvements in the symptoms and signs of disease. One theory is that the basal ganglia–thalamic–cortical system consists of sets of nested oscillators (Montgomery, 2004a). Each oscillator has a fundamental frequency. Therapeutic DBS may resonate with specific oscillators, amplifying the signal-to-noise ratio to improve physiological information processing (Montgomery, 2007b, 2008b; Montgomery and Gale, 2008). The frequency of therapeutically effective DBS for limb function in Parkinson's disease is approximately 140 pps, which is close to the resonant oscillator frequency of the motor cortex–ventrolateral thalamic reentrant circuit.

How these principles apply to efficient and effective DBS programming is unclear. In the absence of any strong theoretical framework that relates DBS frequency to therapeutic effects, clinical experience will have to guide treatment. Consequently, I address the issues of DBS frequency in subsequent descriptions of DBS programming approaches to specific disease categories.

Another implication of stimulation frequency occurs with IPGs that allow the patient or caregiver to adjust the frequency. For example, a patient with Parkinson's disease may find that high-frequency DBS of the STN improves arm and hand function but worsens gait. Alternatively, low-frequency DBS may improve gait but worsen arm and hand function. Thus, the patient can adjust the frequency to improve the desired function when the appropriate IPG is used.

For some DBS systems, the ability of the patient or caregiver to control the DBS stimulation parameters does not exist. Other systems vary in the degree to which the patient and/or caregiver can modify the DBS electrode configurations and stimulation parameters. The choice depends on many factors, such as the ability of patients

and/or caregivers to comply with instructions given by physicians or health care professionals. However, there are certain circumstances in which it is important that the patient and/or caregiver has the ability to control electrode configurations and stimulation parameters. For example, our practice is to routinely use systems that provide some degree of patient and/or caregiver control in patients undergoing thalamic DBS, because of the relatively high incidence of stimulation-induced speech disturbances. In these patients, the DBS can be increased in intensity when limb control takes a higher priority than speech and then lowered when speech is a priority.

We are beginning to take the same approach to patients with Parkinson's disease with significant gait problems. In these patients, high-frequency DBS can be used when upper extremity control is at a premium and low-frequency DBS can be used to facilitate walking and balance control. The problem is that one cannot know ahead of time whether any given patient will need this control. In the case of thalamic DBS, the incidence of speech problems is sufficiently high to warrant implanting DBS systems that provide for patient and/or caregiver control.

Some IPGs allow for the patient and/or caregiver to change the stimulation parameters only, such as frequency (rate), pulse width, or amplitude. However, if these systems do not provide feedback to the patient and/or caregiver regarding the current settings, then these patients and/or caregivers can become confused. Some IPGs allow for a set of predefined electrode configurations and stimulation parameters, and the patient and/or caregiver can select among these settings, thereby avoiding confusion.

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6 Approaches to Programming

Persistence and patience are the keys to successful DBS programming. Several studies show that one of the most common causes of unsuccessful DBS therapy is an inadequately programmed IPG.

Successful programming depends on several factors, including maximizing therapeutic efficacy, minimizing side effects, prolonging battery life, and using your time and effort efficiently. Although published case series and clinical trials report average DBS frequencies, pulse widths, and the most common electrode configurations, the variability among patients limits the use of this information. These average or most common stimulation variables should be considered as starting points for programming and not the endpoints.

There are literally thousands of possible stimulation parameters, referring to frequency, pulse width, and current/voltage, and possible electrode configurations, referring to the combinations of negative and positive contacts. Thus, developing a systematic approach to programming is in your and your patient's best interest. Often, applying the principles of electrophysiology and electronics discussed previously and knowing the regional anatomy around the DBS target (discussed later) will allow you to bypass many combinations and focus on those that have a higher probability for success.

Optimizing Battery Life

Eventually, the IPG battery will run down and need to be replaced. Although IPG replacement is a fairly minor surgical procedure, it is not without risk and expense. Consequently, you should try to select stimulation parameters and electrode configurations that will maximize battery life without compromising clinical effectiveness or increasing side effects. However, how to optimize the battery or charge (when using a rechargeable IPG) is problematic because of the difference between the voltage of the battery in the IPG and the amount of voltage delivered by the constant-*voltage* IPG or the voltage necessary to provide the stimulation current when using the constant-*current* IPG. Most IPGs have special electronics that allow stimulation with voltages greater than the battery voltage; however, this is done at some loss of efficiency. For example, the current drained from the battery to raise the stimulation voltage in the constant-*voltage* IPGs or to raise the voltage necessary for the stimulation current in the constant-*current* IPGs (constant-*current* IPG effective voltage) from 1 V below the battery voltage to the battery voltage is less than the amount of current drained when raising from the battery voltage to 1 V above the battery voltage. Thus, there is a cost for stimulating that requires a voltage greater than the battery voltage. Compounding this problem is the fact that some IPGs have a battery voltage less than the typical stimulation voltages needed for clinical efficacy.

It is highly likely that the less the battery voltage is relative to the typical voltages for constant-*voltage* IPGS or constant-*current* IPG effective voltages and the typical requirements for clinical efficacy, the less efficient the IPG will be.

The degree of loss of efficiency when the stimulation voltage exceeds multiple integers of the battery voltage, in the case of constant-*voltage* IPGs, or constant-*current* IPG effective voltages, is not common or public knowledge. However, one commercially available IPG uses a "voltage-doubling" circuit and this is highly inefficient. Programmers should consult the manufacturer regarding the efficiency trade-offs when exceeding the battery voltage. Some hypothetical examples of how efficiency may be considered are shown in Figure 6.1.

The lack of information regarding loss of efficiency with increasing voltage makes it difficult to provide specific recommendations regarding how to adjust the stimulation current/voltage. In the absence of any better knowledge, I have adopted a programming target stimulation voltage, in the case of constant-*voltage* IPGs, of 3.5 V. This is not to say that the user cannot exceed 3.5 V (or the comparable stimulation current in the case of constant-*current* IPGs). The choice of a target voltage of 3.5 V was based on experience with older IPGs that utilized the "voltage-doubling" electronics and were comparatively less efficient. It is hoped that with further experience with new IPGs, more specific recommendations can be provided based on facts, principles, and experience. The physician or health care professional should consult the manufacturer's information regarding the specific IPGs used and may elect to use a different target voltage.

Here, I describe a general method for adjusting the stimulation parameters, including voltage, pulse width, and frequency. This method is effective for any configuration of

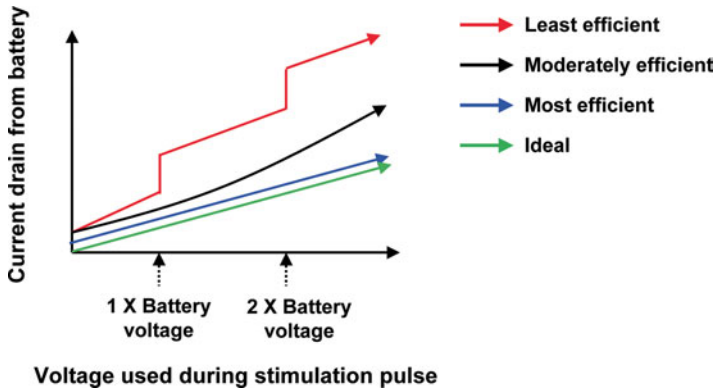


FIGURE 6.1. *Hypothetical method for evaluating battery optimization efficiency. Little information is available to precisely judge the relative efficiency of IPGs with respect to optimizing battery life by minimizing the electrical current drain from the IPG batteries relative to the necessary stimulation parameters. Certainly, the area under the stimulation pulse waveforms affects battery longevity, and the waveforms are affected by the electrical current with each pulse, the pulse width, and the DBS frequency (rate). However, the electronics within the IPG also influence efficiency, particularly when the stimulation voltage in the constant-*voltage *IPG or constant-*current *IPG effective voltage exceed the battery voltage. Some IPGs have a voltage-doubling circuit that is engaged each time the stimulation voltage exceeds some integer multiple of the battery voltage with progressive loss of efficiency (the red tracing). One way to judge the efficiency would be to measure the battery electrical current drain with successive increases in the current/voltage used during stimulation, with all other parameters [pulse width, impedance, and frequency (rate)] held constant. The area between the plot of battery current drain versus voltage stimulation of the actual IPG and the same plot in the ideal IPG (green trace) would be a measure of efficiency.*

negative and positive contacts. Methods for selecting and adjusting configurations of negative and positive contacts are described later.

In addition to voltage demands by stimulation exceeding the battery voltage, multiple negative and positive contacts increase battery drainage, as do increased pulse widths and frequencies. Factors that shorten battery life are provided in the following list, from those that cause the greatest shortening to the least. Note, that the battery life is related to the charge (number of electrons or coulombs) drained from the battery during stimulation. The charge lost is proportional to the area under the DBS pulse, which is a function of the current/voltage, pulse widths, and frequencies. In this case, doubling the pulse width equals doubling of the current/voltage that equals doubling the frequency. Thus, one might ask, How is it possible to differentiate or rank the effects of different parameter changes on battery life? The answer is to determine the usable range for each parameter. DBS frequency typically operates within a more limited range—for example, in some cases ranging from 130 to 185 pps. Thus, moving from one extreme to the other results in less than a doubling of the battery charge loss. Similarly, stimulation current/voltage also operates over a relatively narrow range. Pulse widths often operate over a much greater range and, consequently, moving from one end to the other more than doubles charge loss.

1. Multiple active contacts.
2. In constant-*voltage* IPGs, a stimulation voltage greater than the battery voltage. In the anticipated constant-*current* IPGs, currents requiring associated stimulation voltages greater than the battery voltage.
3. Greater pulse widths.
4. Higher stimulation frequencies.
5. In constant-*voltage* IPGs, stimulation voltages that are less than the battery voltage. In the anticipated constant-*current* IPGs, currents requiring associated stimulation voltages less than the battery voltage are likely to increase the rate of battery use.

These issues may be less of a concern for rechargeable IPGs, although they are still a concern. The same factors that influence battery longevity will also affect how often a recharge is needed, and the risk of a device failure from lack of recharge is proportional to how often the device has to be recharged.

Decisions regarding whether to use a fixed battery device or a rechargeable device depend on a number of factors. In addition to patient and/or caregiver compliance, which includes acts of omission and commission by the patient and/or caregiver such as the tendency to "fiddle" with the device, the physician must consider the worst-case scenario in the event of a device failure for lack of recharge. Cases of serious consequences of device failure have been published for patients with Parkinson's disease. This may be less of a factor for essential tremor. Counterbalancing the risks of a rechargeable system are the advantages in those patients who typically require high currents/voltages, pulse widths, and frequencies (rates), such as patients with dystonia and obsessive–compulsive disorder.

To minimize device electrical current drain, start with the lowest number of active contacts, typically monopolar. Start with the shortest pulse width that has a probability of being effective based on clinical experience, typically 60 μs. Choose the starting

frequency as the slowest in the range expected to be therapeutic. For example, for subthalamic nucleus (STN) DBS for upper extremity function, a reasonable starting frequency would be 130 pps. However, for pedunculopontine nucleus (PPN) DBS [which would be an "off-label" use of a Food and Drug Administration (FDA)-approved device], 40 pps would be reasonable. The current/voltage would initially be set at zero. The first parameters to increase are those that have the least effect on battery life (discussed previously). In constant-*voltage* IPGs, increase the voltage until you achieve a therapeutic effect, but avoid exceeding the battery voltage (discussed later). With constant-*current* IPGs, the relationship between efficiency and preserving battery life is more complicated because the voltage changes as the impedance changes with different electrode configurations. Unless the constant-*current* IPG provides information about the voltage or the impedances from which the voltage can be calculated, avoid stimulation currents that would result in voltages above the battery voltage. If you can determine the impedance and you have control of the electrical current, you can calculate the voltage from Ohm's law (see Eq. 1.1).

The general approach integrating changes in electrode configurations and stimulation parameters is shown in Figure 6.2. The first step, following the monopolar survey, is to start with the electrode configurations suggested by the monopolar survey. Note that in my practice, it is typical to use 90-μs pulse widths and a frequency of 130 pps for the monopolar survey. Typically, one starts with a monopolar configuration because this provides a larger volume of activation. In many institutions, the distal edge of the distal DBS contact is placed at the bottom of the DBS target structure. Consequently, a typical initial configuration is monopolar with the most distal contact being negative. Then an algorithm is used to progress through the various combinations of stimulation parameters until either sufficient symptomatic relief is obtained and one stops or a limiting side effect is encountered. If the latter occurs, one returns to the algorithm for selecting

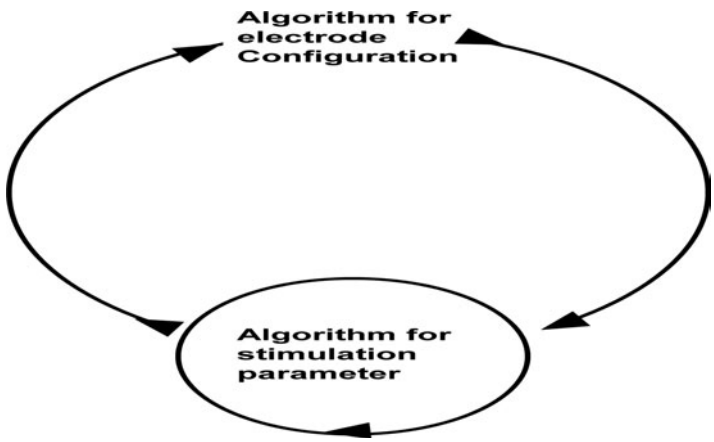


FIGURE 6.2. *Representation of the general scheme of DBS programming. There are two sets of algorithms, the first to select electrode configurations and the second to select stimulation parameters. The second algorithm is nested or embedded in the first. The process is reiterative. An electrode configuration is chosen based on an algorithm or process described in this chapter and chapters 7–9, and then the algorithm for selecting stimulation parameters is executed. Depending on the results, either the patient is doing well or the programmer returns to the algorithm for electrode configurations, chooses a new configuration, and then reenters the algorithm for the stimulation parameters.*

electrode configurations. Once a new electrode configuration is chosen, the process for adjusting the stimulation parameters is reinitialized and then the algorithm is executed until sufficient symptomatic relief or a limiting side effect occurs. If the latter occurs, the process is repeated.

For constant-*voltage* IPGs, increase the voltage until you achieve a therapeutic effect, but avoid exceeding the battery voltage. Note that this may be problematic for IPGs in which the battery voltage is less than the stimulation voltage typically used. At the least, avoid the higher multiples of the battery voltage. For example, if the battery voltage is 3 V and operating at approximately 3 V is unavoidable, try to keep the voltage less than 6 V (two times the battery voltage of 3 V). If you increase the voltage to near the battery voltage without a sufficient clinical response, reduce the voltage and increase the frequency. Then, increase the voltage again until you achieve a therapeutic effect or until you approach the battery voltage. If the clinical response is still insufficient, increase the frequency. If you can no longer increase the frequency, then reduce the voltage and frequency to the minimum and increase the pulse width. Repeat the process as shown in Figure 6.3. Remember that the

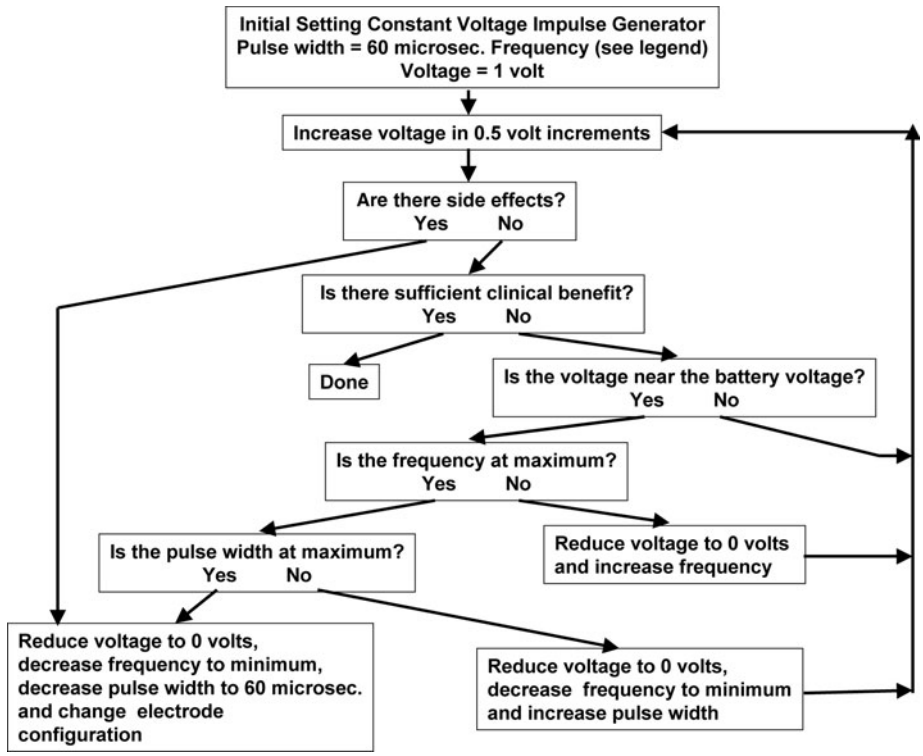


FIGURE 6.3. *How to adjust stimulation parameters for any specific electrode configuration used with constant-*voltage *IPGs. The initial DBS frequency will vary depending on DBS target and disease. For general use in Parkinson's disease, essential tremor, dystonia, Tourette's syndrome, hyperkinetic disorders in general, and cerebellar outflow tremor, the initial frequency will usually be 130 pps. For patients with Parkinson's disease who experience worsening of gait or speech with high high-frequency DBS, the initial DBS frequency can start at 40 pps. For patients with dystonia who show no improvement with the typical high frequencies, DBS of the globus pallidus internal segment at 40 pps or less may be helpful. Pedunculopontine nucleus (PPN) DBS may be employed, and often its initial DBS frequency is 40 pps. DBS for Tourette's syndrome, hyperkinetic disorders in general, and cerebellar outflow tremor as well as PPN DBS are considered to be off-label uses of an FDA-approved device; the FDA has not issued any specific recommendations regarding this technology. In many cases, off-label use is considered standard and accepted therapy and not experimental or investigational.*

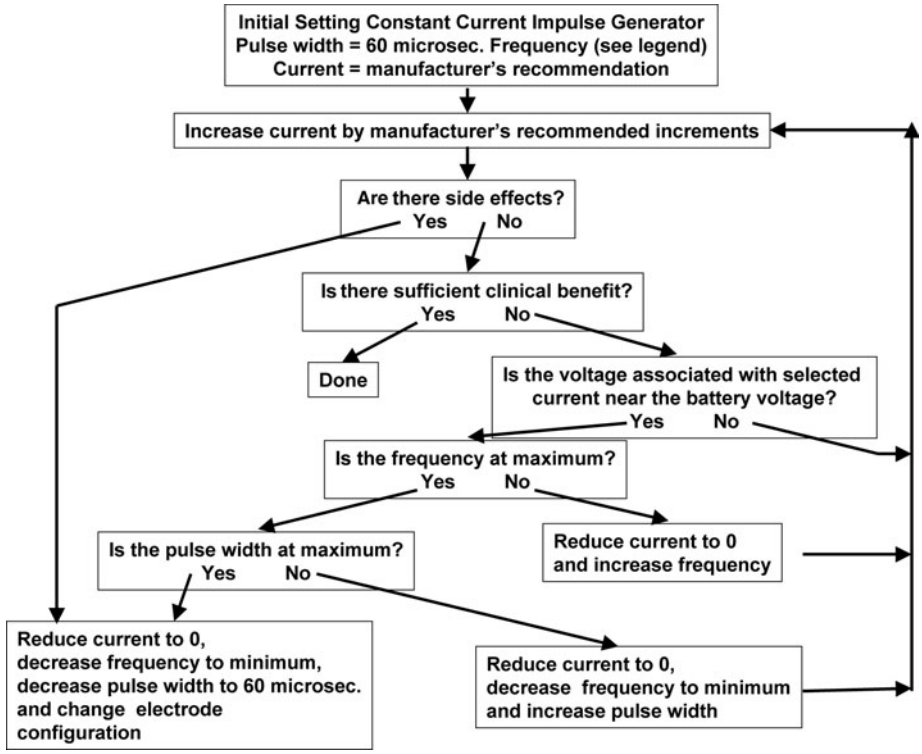
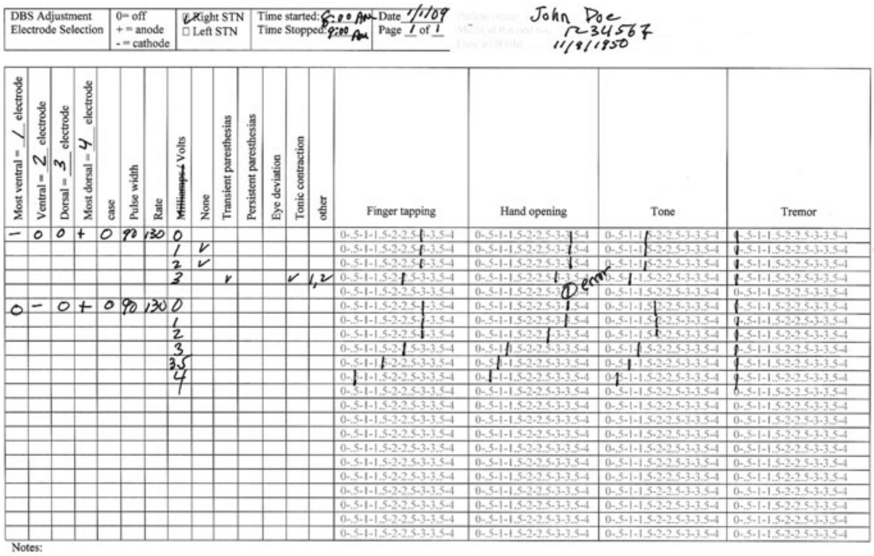


FIGURE 6.4. *How to adjust stimulation parameters for any specific electrode configuration used with constant-*current *IPGs. The initial DBS frequency will vary depending on DBS target and disease. For general use in Parkinson's disease, essential tremor, dystonia, Tourette's syndrome, hyperkinetic disorders in general, and cerebellar outflow tremor, the initial frequency will usually be 130 pps. For patients with Parkinson's disease who experience worsening of gait or speech with high high-frequency DBS, the initial DBS frequency can start at 40 pps. For patients with dystonia who show no improvement with the typical high frequencies, DBS of the globus pallidus internal segment at 40 pps or less may be helpful. PPN DBS may be employed, and often its initial DBS frequency is 40 pps. DBS for Tourette's syndrome, hyperkinetic disorders in general, and cerebellar outflow tremor as well as PPN DBS are considered to be off-label uses of an FDA-approved device; the FDA has not issued any specific recommendations regarding this technology. In many cases, off-label use is considered standard and accepted therapy and not experimental or investigational. Also, no constant-*current *IPGs have received FDA approval.*

battery voltage may differ among the currently commercially available IPGs. Consult the manufacturer's specifications to determine the battery voltage and efficiency for stimulation voltages above the battery voltage for that type of IPG. Figure 6.4 shows how to adjust the stimulation parameters for any specific electrode configuration used with constant-*current* IPGs.

For most patients, several DBS programming sessions will be required to determine the most effective combination of parameters, electrode configurations, and medications. You will often need to refer to previous sessions to review progress. Consequently, you should assess the symptoms and document the clinical responses carefully (see Chapter 10). Templates of the forms used during programming sessions are shown in Appendix 2. A hypothetical example is shown in Figure 6.5.

The general goals of DBS programming are to control symptoms and prevent side effects. Often, symptom control means stimulating a sufficient volume and number of neural elements. Consequently, as described in the subsequent algorithm,



DBS Adjustment Electrode Selection	0= off + = anode - = cathode	☑ Right STN ☐ Left STN	Time started: 8:00 AM Time Stopped: 9:00 AM	Date 1/1/09 Page 1 of 1	John Doe R-34567 11/9/1950

Most ventral = 1 electrode	Ventral = 2 electrode	Dorsal = 3 electrode	Most dorsal = 4 electrode	case	Pulse width	Rate	~~Milliamps~~/ Volts	None	Transient paresthesias	Persistent paresthesias	Eye deviation	Tonic contraction	other	Finger tapping	Hand opening	Tone	Tremor
−	0	0	+	0	90	130	0							0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
							1	✓						0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
							2	✓						0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
							3		✓			✓	1,2	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
0	−	0	+	0	90	130	0							0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
							1							0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
							2							0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
							3							0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
							3.5							0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
							4							0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

FIGURE 6.5. *A hypothetical example of a programming session. The electrode contacts are labeled "most ventral," "ventral," "dorsal," and "most dorsal." The DBS lead used in this hypothetical example had a convention for naming contacts such that the first contact or most distal is contact 1 and the subsequent contacts moving proximally are contacts 2, 3, and 4, respectively. These IPG naming conventions were entered into the form. DBS of the STN may be associated with potential side effects described as "transient paresthesias," "persistent paresthesias," "eye deviation," and "tonic contraction" of muscles. An additional category, "other," allows for identification of other side effects or to specify one of the side effects checked. The patient in this hypothetical example has Parkinson's disease, so the following clinical signs were assessed using a grading scale described in Appendix 2. The scales are based on a 0 to 4 rating, with 0 being normal. As can be seen in this example, the first electrode configuration, monopolar with contact 1 negative, produced tonic muscle contraction. Consequently, a new electrode configuration was determined. In this second configuration, the subject was able to have good control of the symptoms. However, the most optimal control required 4 V, which was higher than the IPG battery voltage. Therefore, trial of another set of stimulation parameters would be indicated. These templates have the advantage of a visual analogue scale that is easy to interpret. In addition, the data for multiple settings can be seen at once.*

you will probably begin to enlarge and intensify the electrical field and to use monopolar, wide bipolar, and multiple cathodes. Conversely, smaller or less intense electrical fields may be needed to prevent side effects. In these cases, narrow bipolar or "bracketed" tripolar configurations may be used. In a bracketed configuration, two anodes flank a single cathode.

The Special Case of the U-Shaped Response

Symptoms typically improve as the electrical current/voltage is increased. Occasionally, however, increasing the electrical current/voltage further may worsen symptoms, producing the so-called "U-shaped" response. In thalamic, STN, or globus pallidus internal segment (GPi) DBS, where the negative electrode contacts are near the corticospinal track, this worsening can be the result of involving the corticospinal tract. This involvement is apparent when continued increases in the electrical current/voltage result in tonic muscle contractions. However, some patients may not experience tonic muscle contraction with higher electrical current/voltages, suggesting that spread of the electrical field to the corticospinal tract is not the mechanism of the U-shaped response (Montgomery and Sillay, 2008) (see Commentary 6.1).

The U-shaped response has two implications for DBS programming. First, consider the case where the range of electrical current/voltage necessary to provide the most optimal electrical current/voltage is small. For a hypothetical example, neither a current/voltage of 0.5 ma/2 V nor one of 1.5 ma/3 V may be effective, whereas that of 1 ma/2.5 V would be effective. If the programmer is not careful, he or she may skip the most optimal parameters (Figure 6.6). Second, if the programmer starts with stimulation parameters associated with the upward slope of the U-shaped curve, he or she could falsely conclude that there are no stimulation parameters that are optimal (Figure 6.7).

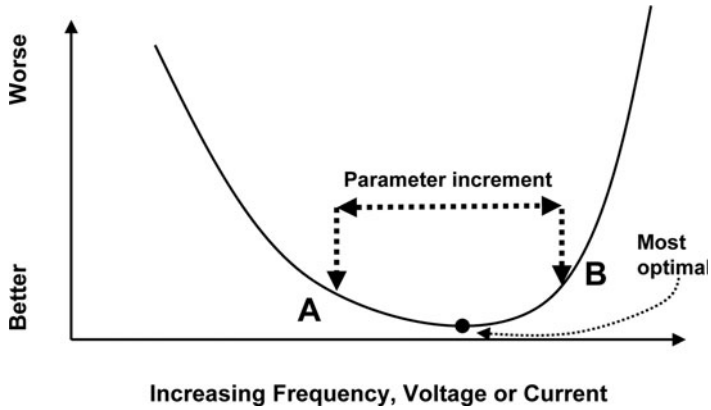


FIGURE 6.6. *Hypothetical example of a U-shaped response where the patient initially gets better with increasing stimulation parameters and then gets worse. If you make too great a change, you may miss the optimal stimulation parameter. For example, consider the case in which the programmer initially sets the parameters at A. The patient appears to improve. Next, the programmer jumps to point B for the stimulation parameters, and the patient appears to worsen. The programmer may elect to go back to the parameters at point A. However, in doing so, the programmer would miss the most optimal set of DBS parameters.*

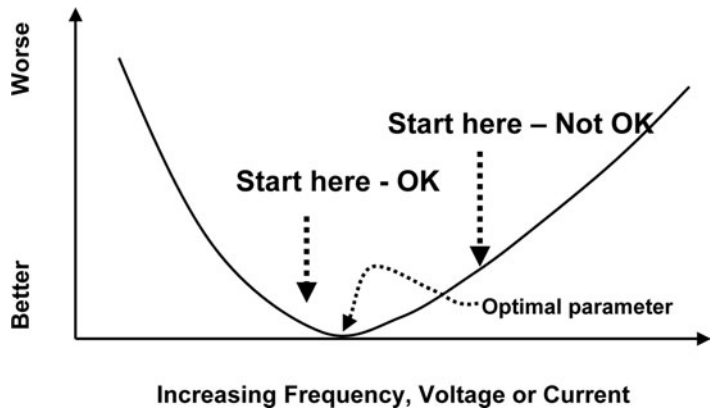


FIGURE 6.7. *Hypothetical example of a U-shaped response where the patient initially gets better with increasing stimulation parameters and then gets worse. If the programmer starts to the left of or less than the most optimal parameters, he or she will see improvement as the parameters are increased. However, if the programmer starts to the right or more than the most optimal parameters, he or she will see the patient worsening and could falsely conclude that there would not be any optimal set of parameters.*

Commentary 6.1. ***The Paradox of Worsening Function with Increasing Strength of DBS: The U-Shaped Response***

The U-shaped response occurs when increasing the strength of DBS initially improves motor function and then worsens it. The strength of DBS can be increased by increasing the frequency in pulses per second, or the current/voltage (current in the case of constant-*current* IPGs and voltage in the case of constant-*voltage* IPGs). If you follow the suggested algorithm and first increase the current/voltage while keeping the frequency constant, you are more likely to detect this U-shaped response.

This response has at least three practical implications. First, you should increase the voltage in small increments, on the order of 0.5 V with constant-*voltage* stimulators and in milliampere increases as recommended by manufacturers' specifications with the anticipated constant-*current* stimulators. Second, it is important to begin with lower current/voltages. Increasing the strength in larger increments or beginning with higher currents/voltages increases the risk of missing the U-shaped response, and you might miss the optimal parameters.

The U-shaped response has important implications for the therapeutic mechanisms of action of DBS. The worsening of symptoms with DBS in patients with Parkinson's disease may be specific to the region of the GPi being stimulated. In fact, some authors have suggested that DBS of the dorsal GPi is prokinetic (improving movement), whereas stimulation of the ventral GPi is antikinetic (worsening movement). One alternative explanation is that the worsening of symptoms is caused by the stimulation current spreading to the internal capsule, which is more likely with stimulation of the ventral GPi. Studies show that DBS of the STN can worsen parkinsonian symptoms but without spread of excessive electrical current to the internal capsule (Montgomery and Sillay, 2008). This raises doubts about a prokinetic dorsal GPi and an antikinetic ventral GPi.

Theories that posit suppressed neuronal activity as a mechanism of action are hard-pressed to explain why further suppression, such as that caused by increasing stimulation, would cause the recurrence or worsening of parkinsonian symptoms. This difficulty is a problem, whether the suppression was cause by presynaptic release of inhibitory neurotransmitters, depolarization blockage, exhaustion of presynaptic excitatory neurotransmitters, or increased accumulation of adenosine (Bekar et al., 2008).

The Systems Oscillator theory, which conceives the basal ganglia–thalamic–cortical system as a set of nested and interconnected, polysynaptic reentrant oscillators (Montgomery, 2004a), can explain this paradoxical response. Collections of neurons in the anatomical structures represent nodes in the oscillators. Neurons within each node do not fire with every cycle of oscillatory activity, but they fire probabilistically such that the average discharge frequency of an individual neuron is less than the frequency of the oscillator. Thus, the neurons operate within a specific range of probability of firing that is influenced by overall excitability.

(*continued*)

Commentary 6.1 ***(continued)***

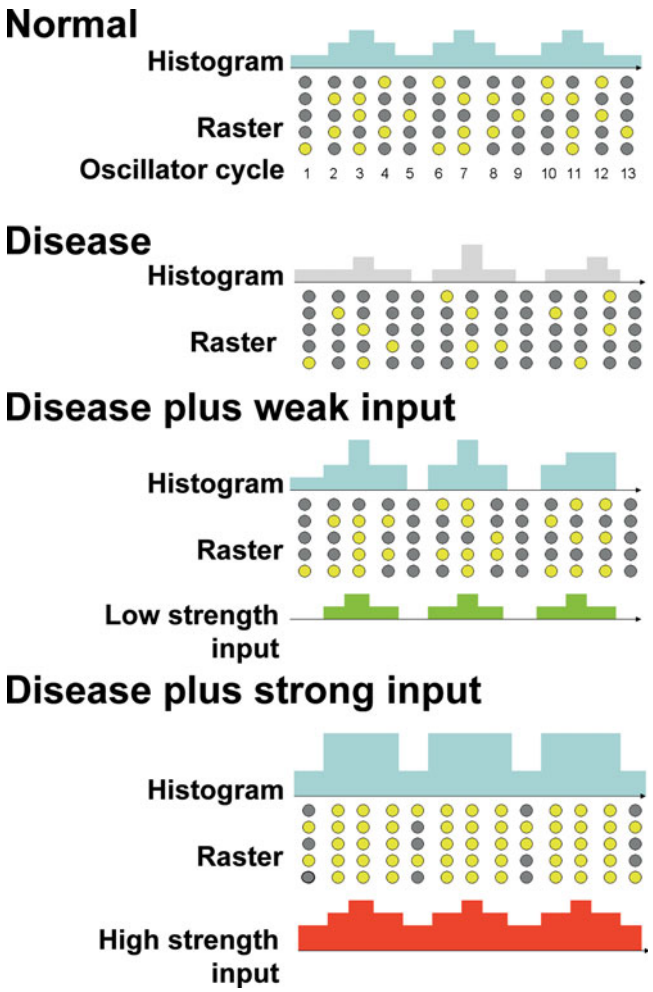


FIGURE 6.8. *Hypothetical illustration of a possible mechanism underlying the U-shaped response to DBS. Each part of the figure contains a raster and a histogram. The raster represents five neurons, some of which discharge during each cycle. A gray circle indicates no discharge, and a yellow circle indicates a neuronal discharge. The histogram represents the total number of neurons discharging in each cycle of the oscillator. Assume that a sinusoidally varying normal signal gradually increases and then decreases the probability of the neuron discharging. In disease, the probability of neurons discharging is reduced; consequently, the information in the neuronal discharges degrades over time. This degradation is reflected in the difference in the histograms between the normal and disease conditions. The degraded information results in the symptoms and signs of the disease. Next, assume a weak input, such as therapeutic DBS, that increases the neuronal discharge probability in waxing and waning pattern at the same frequency of the inherent changes under the normal condition. In this case, the information represented in the histogram is more like the normal condition than the disease condition. This case is associated with improved symptoms and signs. Next, assume that the input signal, such as high current/voltage DBS, greatly increases the probability of a neuronal discharge. Now, nearly all the neurons are discharging with each cycle, and the histogram saturates and loses information, in contrast to the normal histogram*

DBS activates the output of neurons in the stimulated target, as well as afferent axon terminals and axons in passage. DBS is highly inefficient, with less than 10% of DBS pulses resulting in a neuronal response (Montgomery,

2006). Consequently, increasing the strength of DBS may increase the excitability at a specific carrier frequency. This frequency in turn resonates with and amplifies the signal generated in the basal ganglia–thalamic–cortical system and improves function, just as an AM radio becomes tuned to the broadcast frequency. However, if the DBS stimulation-induced excitability of the neurons becomes too great, the signal deteriorates. In a sense, the signal saturates the structures interfering with the modulation of the neuronal spike train necessary to encode information. This concept has been verified in computational simulations (Montgomery and Sillay, 2008).

Figure 6.8 shows a hypothetical example. The rasters consist of five neurons. At each cycle of the oscillation, some or none of the neurons discharge. In the normal condition, the number of neurons discharging at each point in time gradually increases and decreases. This process is represented in the histogram, which is the sum of neurons discharging in each column, and the columns representing each cycle of the oscillator. This would be analogous to the proper modulation of neuronal activity over time to drive behaviors. Next, consider the circumstance of a disease that reduces the probability of a neuron discharging with each cycle of the oscillator. The histogram reflects a degraded signal that is very dissimilar to the normal pattern. Now consider the circumstance in which there is a weak input signal, analogous to a relatively inefficient DBS but associated with optimal clinical response, at the same frequency as the normal variations represented in the histogram of the normal condition. This input increases the probability of a neuron discharging with each cycle. The new histogram is more like the normal histogram. If the input signal is too strong, analogous to DBS stimulation parameters on the upward slope of the U-shaped curve, then the probability of a neuron discharging is too high and the rasters and histogram "saturate." The resulting signal is less like the normal condition compared to the condition of a weak input signal. Thus, the input of a weak signal improves the neuronal activity, thereby improving symptoms over the disease condition. The input of the strong signal degrades the neuronal activity and the symptoms worsen, resulting in a U-shaped curve.

Optimizing Therapeutic Effect and Minimizing Side Effects

The methods described in Figures 6.3 and 6.4 for adjusting stimulation parameters are appropriate for any specific configuration of negative and positive contacts. The methods described here relate to selecting and adjusting the configuration of negative and positive contacts to achieve efficacy and minimize side effects. Therapeutic efficacy is primarily related to the location of the stimulation electrical field and, consequently, precise targeting is critical. Secondary factors affecting therapeutic efficacy relate to the volume of brain tissue activated by the electric field and the number of neural elements within the electric field. For any single cathode, monopolar stimulation provides the electrical field with the greatest volume, whereas wide bipolar stimulation gives the most intense electrical field, which relates to the current density around the cathode (see Chapter 3).

These discussions of electrode configurations assume that the DBS lead consists of a linear array along the long axis of the DBS lead, as depicted in Figure 6.9. This assumption is true for commercial DBS leads and those in clinical trials. The general principles described here also apply to other types of DBS leads, although the specific algorithms may differ. You should consult the manufacturer of the DBS leads you intend to use.

Side effects are caused primarily by unintentionally stimulating undesired neural elements. Consequently, the largest electrical fields, such as those provided by monopolar cathodes, are the most likely to produce side effects, and narrow bipolar stimulation is the least likely.

The choice of negative contacts has a major impact on both efficacy and the risk of side effects. Different contacts lie either closer to or farther from the intended targets or from the unintended neural elements. Thus, judiciously choosing the active cathodes can maximize efficacy and minimize side effects. This choice depends on the regional anatomy of the leads placed in individual patients.

Some commercially available and anticipated IPGs allow for partitioning the stimulation current/voltage among different electrodes. For example, the system can be configured so that the DBS pulse on one contact is 5 ma or 3 V while another contact can have 3 ma or 1 V. Some commercially available IPGs interleave these different pulses rather than truly partitioning the stimulation current/voltage among the contacts simultaneously (see Figure 3.23). Unfortunately, experience using such partitioned stimulations is insufficient to warrant any conclusions as to relative efficacy. However, the same fundamental principles discussed in this book apply. Until more direct experience is gained, I suggest avoiding partitioning the stimulation currents/voltage unless the more traditional approaches have been tried. Should

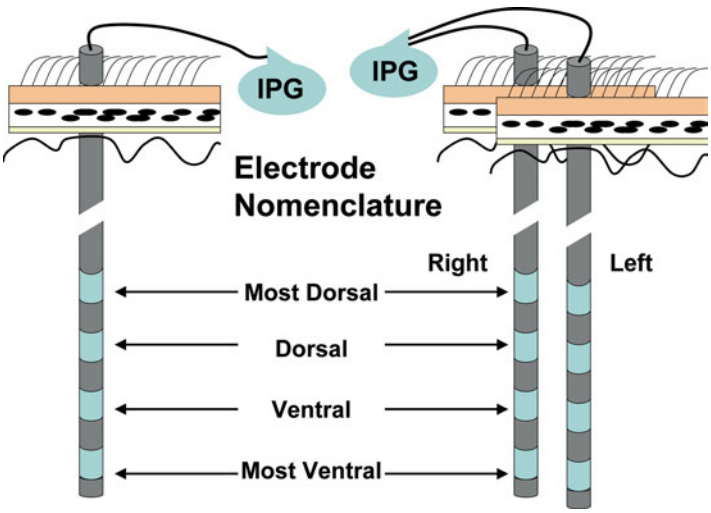


FIGURE 6.9. *Nomenclature of a DBS lead with four contacts. Manufacturers often number the contacts, but the conventions vary. The discussion of electrode configurations assumes that the DBS lead consists of a linear array along the long axis of the DBS lead, as depicted in the figure. This assumption is true for commercially available DBS leads and those anticipated to become available in the near future. The general principles described here also apply to other types of DBS leads, although the specific algorithms may differ. You should consult the manufacturer of the DBS leads you intend to use.*

the traditional approaches fail, particularly when side effects are the problem, one could proceed from narrow bipolar configurations to a multipolar configuration in which one of the electrodes is stimulated with a lower current/voltage. Potential circumstances in which partitioned stimulation parameters may be helpful are discussed in Chapters 7–9 on the regional anatomies of the DBS targets.

Algorithm for Selecting Electrode Configurations

The following algorithm is an attempt to systematize the process of selecting electrode configurations. Analyzing the results of the monopolar survey first can reduce the number of configurations you need to consider, allowing you to bypass some stages in the algorithm. However, if you are not confident inferring initial electrode configurations based on the monopolar survey, you can work through the complete algorithm. This algorithm is presented with check boxes and spaces for comments in Appendix 3 and can be photocopied as needed. The algorithm is particularly useful for patients whose parameters are difficult to program. Checking off the various steps helps to document and summarize the findings for individual patients, ensuring that every configuration has been tried without duplication.

The general approaches embodied in the algorithm are as follows: (1) a systematic approach is used so that potential electrode configurations and stimulation parameters are not overlooked; (2) efficacy is addressed by first using monopolar, then wide bipolar, and then multiple negative contacts; and (3) side effects are addressed by going from monopolar to progressively narrower bipolar and then finally to tripolar configurations. Many of the steps in the algorithm can be bypassed for greater efficiency by careful analysis of the monopolar survey in light of the regional anatomy surrounding the DBS leads, as will be discussed later. Chapters 7–9 catalogue various side effects based on the DBS site. However, the same side effects can be produced by DBS at different sites. Appendix 1 is organized based on the side effect symptom and site and then directs the reader to the appropriate section for a discussion of the side effects and possible means to resolve them.

The numbering conventions for the contacts used here assume that the DBS lead contains four potential cathodes (Figure 6.9). Unfortunately, there has been an undisciplined proliferation of numbering conventions. For example, one DBS system configuration uses contacts numbered 0–3 for the right side DBS lead and contacts numbered 8–11 for the left DBS lead. Other IPGs number the right-sided contacts 1–4 and the left-sided contacts 5–8. And there are even more complicated numbering schemes. Rather than risk compounding the confusion, I refer to the contacts as "most ventral," "ventral," "dorsal," and "most dorsal" (see Figure 6.9). Electrode configurations are described as monopolar (DBS lead contacts as cathodes and the IPG as anode), wide bipolar (both anode and cathodes on the DBS lead and there are two contacts between the anode and the cathodes), close bipolar (both anode and cathodes on the DBS lead and there is one contact between the anode and the cathodes), and narrow bipolar (both anode and cathodes on the DBS lead and there are no contacts between the anode and cathodes).

An example of an applied algorithm is described here. The algorithm relates to electrode configurations, but within this algorithm are references to adjusting

stimulation parameters. Note that this algorithm does not include approaches for parsing out different stimulation currents/voltages among the contacts of the same DBS lead (such as interleaved DBS) because there is insufficient experience to warrant specific recommendations. However, based on the principles described here, one potential step in the algorithm to explore such parsing of stimulation current/voltage may be at the stage following multiple anodes where side effects still limit reaching therapeutic efficacy. The parsing of the stimulation current/voltage can be based on the differential results of the various contacts during the monopolar survey or by assigning the lower stimulation current/voltage to a specific contact based on the regional anatomies described here.

Some of these steps may be bypassed based on the results of the monopolar survey. However, when in doubt, following the algorithm may help to ensure that the potentially useful combinations have been explored. More specific forms suitable for patient annotation and documentation are available in Appendix 3, which you may wish to photocopy and enlarge. (An electronic version with hyperlinks for more efficient electronic maneuvering through the algorithm is available at www.XXXXXXX.. You may wish to download this electronic form and reuse it for each patient, storing a copy in the patient's medical record.)

Step 1 Start
- Single cathode (−) monopolar stimulation
- Most ventral contact cathode (−); case anode (+)
- Increase parameters as shown in Figures 6.3 and 6.4
  - Side effects: Go to step 1.1
  - Lack of efficacy: Go to step 1.1

Step 1.1 Single cathode (−) monopolar stimulation
- Ventral contact cathode (−); case anode (+)
- Increase parameters as shown in Figures 6.3 and 6.4
  - Side effects: Go to step 1.2
  - Lack of efficacy: Go to step 1.2

Step 1.2 Single cathode (−) monopolar stimulation
- Dorsal contact cathode (−); case anode (+)
- Increase parameters as shown in Figures 6.3 and 6.4
  - Side effects: Go to step 1.3
  - Lack of efficacy: Go to step 1.3

Step 1.3. Single cathode (−) monopolar stimulation
- Most dorsal contact cathode (−); case anode (+)
- Increase parameters as shown in Figures 6.3 and 6.4
  - Side effects: Go to step 2.0
  - Lack of efficacy: Go to step 2.0

Step 2.0 Wide bipolar polar stimulation
- Most ventral contact cathode (−); most dorsal contact anode (+)
- Increase parameters as shown in Figures 6.3 and 6.4
  - Side effects: Go to step 2.1

Lack of efficacy: Go to step 2.1

Step 2.1 Wide bipolar polar stimulation
Most ventral contact anode (+); most dorsal contact cathode (−)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 5.0
Lack of efficacy: Go to step 3.0

Step 3.0 Multiple cathodes (−) monopolar stimulation
Most ventral and ventral contacts cathode (−); case anode (+)
Check therapeutic impedances
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 3.1
Lack of efficacy: Go to step 3.1

Step 3.1 Multiple cathodes (−) monopolar stimulation
Ventral and dorsal contacts cathode (−); case anode (+)
Check therapeutic impedances
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 3.2
Lack of efficacy: Go to step 3.2

Step 3.2 Multiple cathodes (−) monopolar stimulation
Dorsal and most dorsal contacts cathode (−); case anode (+)
Check therapeutic impedances
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 4.0
Lack of efficacy: Go to step 4.0

Step 4.0 Wide multiple cathode (−) bipolar stimulation
Most ventral and ventral contacts cathode (−)
Most dorsal contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 4.1
Lack of efficacy: Go to step 4.1

Step 4.1 Wide multiple cathode (−) bipolar stimulation
Most dorsal and dorsal contact cathodes (−)
Most ventral contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 5.0
Lack of efficacy: Check system for hardware failure, confirm correct DBS lead location. Note that interleaved configurations and parameters have not been recommended at this point in the algorithm for two reasons. First, there is insufficient experience with this method. Second, based on principle, the most likely use of the interleaved stimulation will be to deal with side effects, which are not the issue at this point in the algorithm. Furthermore, monopolar and wide bipolar configurations are most likely to have the highest efficacy and would already have been tested by this point in the algorithm.

Step 5.0 Close single cathode (−) bipolar stimulation
Most ventral contact cathode (−); dorsal contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 5.1
Lack of efficacy: Go to step 5.1

Step 5.1 Close single cathode (−) bipolar stimulation
Ventral contact cathode (−); most dorsal contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 5.2
Lack of efficacy: Go to step 5.2

Step 5.2 Close single cathode (−) bipolar stimulation
Most dorsal contact cathode (−); ventral contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 5.3
Lack of efficacy: Go to step 5.3

Step 5.3 Close single cathode (−) bipolar stimulation
Dorsal contact cathode (−); most ventral contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 7.0
Lack of efficacy: Go to step 6.0

Step 6.0 Close multiple cathodes (−) bipolar stimulation
Most ventral and ventral contacts cathode (−); dorsal contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 6.1
Lack of efficacy: Go to step 6.1

Step 6.1 Close multiple cathodes (−) bipolar stimulation
Ventral and dorsal contacts cathode (−); most dorsal contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 6.2
Lack of efficacy: Go to step 6.2

Step 6.2 Close multiple cathodes (−) bipolar stimulation
Most dorsal and dorsal contact cathodes (−); ventral contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 6.3
Lack of efficacy: Go to step 6.3

Step 6.3 Close multiple cathodes (−) bipolar stimulation
Dorsal and ventral contacts cathodes (−); most ventral contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 7.0
Lack of efficacy: Check system for hardware failure, confirm correct DBS lead location. Note that interleaved configurations and parameters have not been recommended at this point in the algorithm for two reasons. First, there is insufficient experience with this method. Second,

based on principle, the most likely use of the interleaved stimulation will be to deal with side effects, which are not the issue at this point in the algorithm. Furthermore, monopolar, wide bipolar, and close bipolar configurations are most likely to have the highest efficacy and would already have been tested by this point in the algorithm.

Step 7.0 Narrow single cathode (−) bipolar stimulation
Most ventral contact cathode (−); ventral contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 7.1
Lack of efficacy: Go to step 7.1

Step 7.1 Narrow single cathode (−) bipolar stimulation
Ventral contact cathode (−); dorsal contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 7.2
Lack of efficacy: Go to step 7.2

Step 7.2 Narrow single cathode (−) bipolar stimulation
Dorsal contact cathode (−); most dorsal contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 7.3
Lack of efficacy: Go to step 7.3

Step 7.3 Narrow single cathode (−) bipolar stimulation
Ventral contact cathode (−); most ventral contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 7.4
Lack of efficacy: Go to step 7.4
Side effect: Go to step 7.4
No efficacy: Go to step 7.4

Step 7.4 Narrow single cathode (−) bipolar stimulation
Dorsal contact cathode (−); ventral contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 7.5
Lack of efficacy: Go to step 7.5
Side effect: Go to step 7.5
No efficacy: Go to step 7.5

Step 7.5 Narrow single cathode (−) bipolar stimulation
Most dorsal contact cathode (−); dorsal contact anode (+)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: Go to step 8.0
Lack of efficacy: Check system for hardware failure, confirm correct DBS lead location

Step 8.0 Narrow multiple anodes (+) tripolar stimulation
Dorsal and most ventral contacts anodes (+); ventral contact cathode (−)
Increase parameters as shown in Figures 6.3 and 6.4

Side effects: Go to step 8.1
Lack of efficacy: Go to step 8.1

Step 8.1 Narrow multiple anodes (+) tripolar stimulation
Most dorsal and ventral contacts anodes (+); dorsal contact cathode (−)
Increase parameters as shown in Figures 6.3 and 6.4
Side effects: At this point, interleaved configurations and parameters should be tried. The stimulation current/voltage can be apportioned based on the side effect profile and efficacy. For example, if stimulation of the most ventral contact provided greater efficacy but with significant side effects, whereas the ventral contact produced less efficacy but no side effects, the first step would be to apply the maximum stimulation current/voltage tolerated on the most ventral contact and then the maximum stimulation current/voltage tolerated on the ventral contact and determine whether this resulted in sufficient efficacy without significant side effects. If this fails, check system for hardware failure, confirm correct DBS lead location.
Lack of efficacy: Check system for hardware failure, confirm correct DBS lead location

7 Approach to Subthalamic Nucleus

Regional Anatomy of the Subthalamic Nucleus

The subthalamic nucleus (STN) lies near the junction of the diencephalon and mesencephalon. It is just ventral to the thalamus, just lateral to the brachium conjunctivum and red nucleus, and medial and dorsal to the internal capsule. These structures are important because inappropriate stimulation causes side effects. For example, just dorsal and posterior to the STN lies the ventrointermediate and ventrocaudal nuclei of the thalamus. The thalamic nuclei relay somatosensory information from the periphery through the medial lemniscus and spinothalamic tracts, which ascend just posterior to the STN, to the cerebral cortex. Electrical fields spreading to ascending sensory medial lemniscus and spinothalamic pathways behind the STN produce paresthesias. The brachium conjunctivum contains fibers running from the deep cerebellar nuclei to the ventrointermedius nucleus of the thalamus. Inadvertent stimulation of the brachium conjunctivum can cause ataxia and loss of balance. The red nucleus lies in the brachium conjunctivum, and the exiting axons from the oculomotor nucleus run within the red nucleus. Electrical fields spreading to these structures can result in disconjugate gaze and diplopia. Stimulating the internal capsule laterally or dorsally can cause tonic muscle contractions.

Side Effects Created by the Position of the DBS Lead Relative to the Subthalamic Nucleus

DBS Lead Too Medial

The side effects of DBS are related directly to stimulation of structures near the STN. If the DBS lead is too medial, the electrical current will spread to the brachium conjunctivum, which is the cerebellar outflow to the ventral intermediate thalamus and motor cortex. The symptoms will include ataxia. Also, the nerve roots of the oculomotor nucleus run from the midline laterally past the red nucleus before turning medially to exit in the interpeduncular fossa. Stimulation of the oculomotor nerve roots can result in diplopia.

Often, the effect of the DBS lead being too medial can be corrected by using the more dorsal contacts in either a monopolar or bipolar configuration because the DBS lead is often positioned laterally to medially in the coronal plane (Figure 7.1). Using more dorsal contacts pulls the current laterally as it moves dorsally. Alternatively, initially wide bipolar or, if necessary, narrower bipolar configurations can be used to shrink the electrical field to pull it away from the brachium conjunctivum, oculomotor nerve roots, or both. However, such approaches may be limited because the

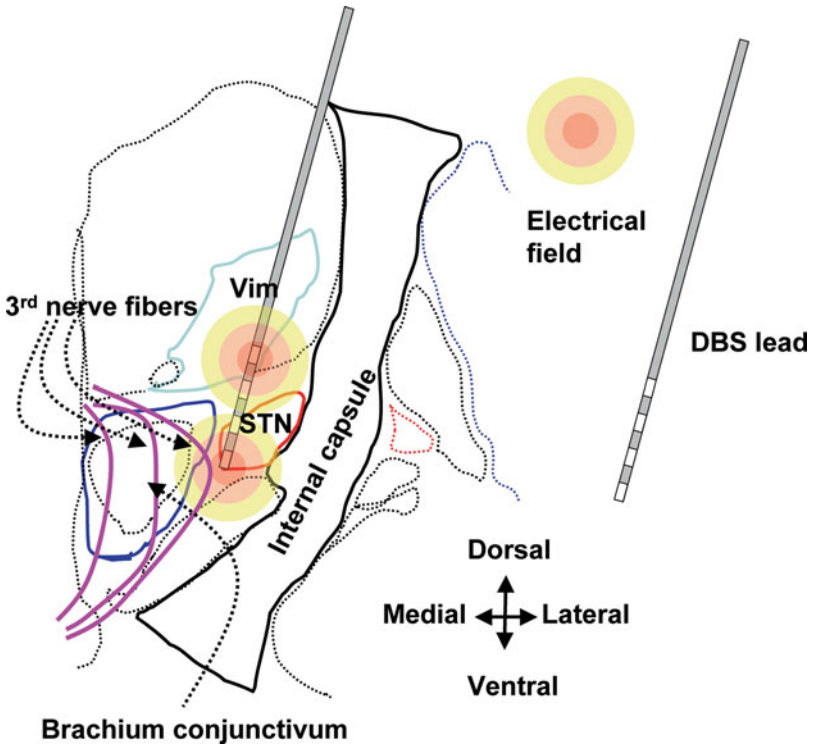


FIGURE 7.1. *Coronal view of the STN 4 mm anterior to the midpoint of the line connecting the anterior and posterior commissure (AC–PC line). The subthalamic nucleus (STN) is outlined in red, the ventrointermediate nucleus of the thalamus (Vim) is outlined in green, the brachium conjunctivum (also containing the red nucleus) is outlined in blue, and the internal capsule is outlined in solid black (see Appendix 2 for a discussion of the various nomenclatures of the thalamic subnuclei). The ventrocaudal (not shown) thalamic nuclei are dorsal and posterior to the STN. The brachium conjunctivum is just medial and slightly posterior to the STN, and the internal capsule is lateral and ventral. Also shown are the nerve fibers exiting the oculomotor nucleus to form the third cranial nerve. The DBS lead in this case is too medial, causing activation of the third nerve and thus producing diplopia when the most ventral contact is used as the negative contact. In addition, spread of electrical activation could affect the cerebellar outflow fibers, causing ataxia. One response would be to move the electrical field more dorsal away from the third nerve fibers and the brachium conjunctivum. However, cathodal stimulation of the most dorsal contact could activate the thalamus, leading to paresthesias. (Adapted from Schaltenbrand and Wahren, 1977.)*

most effective stimulation site may be more ventral. If these measures fail and efficacy is insufficient, another approach would be to use multiple cathodes in an interleaved manner such that a lower stimulation current/voltage is applied to the more ventral contact (note that this does not necessarily mean the "most ventral" contact; see Figure 6.9) and a greater stimulation current/voltage is applied to more dorsal contacts (note that this does not necessarily mean the "most dorsal" contact; see Figure 6.9).

DBS Lead Too Anterior

The internal capsule borders the STN on the lateral, ventral, and anterior sides. Stimulation spreading to the internal side can produce contralateral tonic muscle contractions. The results of the monopolar survey can help determine whether the DBS lead is too deep, too lateral, or too anterior. For a DBS lead that is too anterior,

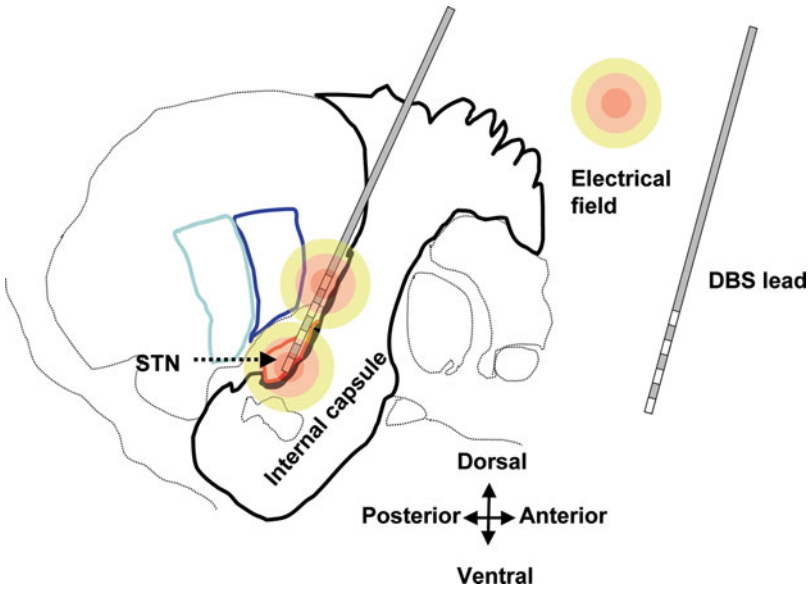


FIGURE 7.2. *A sagittal section 17 mm lateral showing the AC–PC line of the STN (outlined in red) with a DBS lead that is too anterior. Electrical stimulation spreads to the internal capsule (outlined in black), causing muscle contractions. Note that the distance between the most ventral contact and the internal capsule and the distance between the most dorsal contact and the internal capsule are nearly the same. This similarity means that the threshold for muscle contraction will be approximately the same for monopolar stimulation through the most dorsal and most ventral contacts and suggests that a DBS lead is too anterior. The most effective way to prevent muscle contractions when the DBS lead is too anterior is to use bipolar configurations, beginning with wide bipolar and progressing to narrow bipolar stimulation, as necessary. (Adapted from Schaltenbrand and Wahren, 1977.)*

the threshold of tonic contraction through the most dorsal cathode is similar to the threshold through the most ventral cathode because the DBS lead is often parallel to the internal capsule anteriorly (Figure 7.2). The most effective way to prevent muscle contractions when the DBS lead is too anterior is to use bipolar configurations, beginning with wide bipolar and progressing to narrow bipolar as necessary.

DBS Lead Too Ventral

To prevent muscle contractions when the DBS lead is too ventral, stimulation should be delivered through the more dorsal leads (Figure 7.3). Most often, you would start with monopolar stimulation and progress to wide bipolar and then to narrow bipolar stimulation, as necessary. This circumstance may be appropriate for partitioning the stimulation current/voltage among the electrode contacts. For example, stimulation through the most ventral contact is most effective in producing a clinical response but produces side effects. Stimulation through the more dorsal contact does not produce sufficient benefit but does not produce as many side effects. One could stimulate both through the most ventral contact at a reduced stimulation current/voltage and then through a more dorsal contact at a higher stimulation current/voltage. However, see Figure 3.23 for caveats in the case of IPGs that interleave the partitioned stimulation parameters. (Note that the terms *more ventral* or *more dorsal* do not necessarily mean the "most ventral" contact or "most dorsal" contact, respectively;

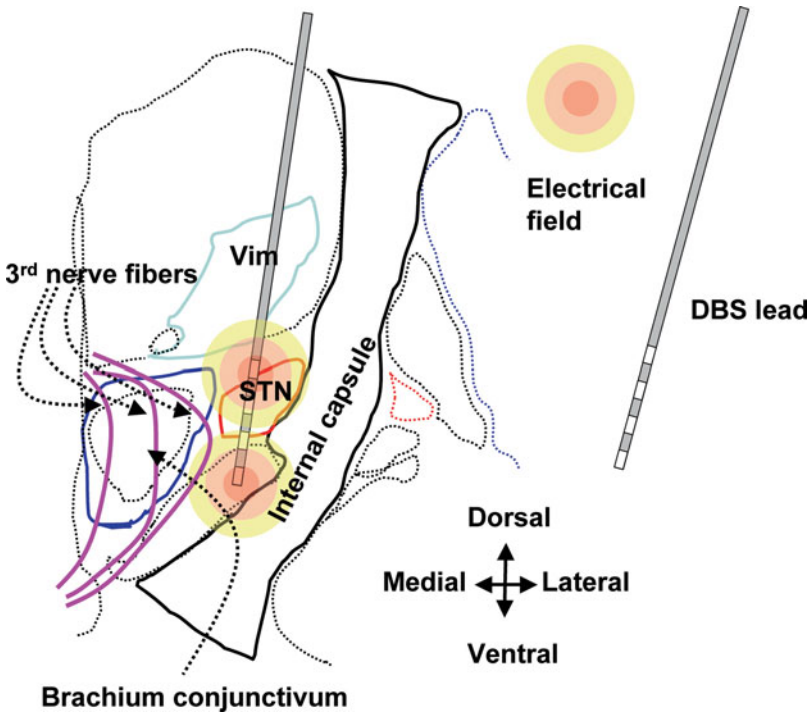


FIGURE 7.3. *Coronal view of the STN 4 mm anterior to the midpoint of the line connecting the anterior and posterior commissure (AC–PC line). The STN is outlined in red, the ventrointermediate nucleus of the thalamus (Vim) in green, the brachium conjunctivum (also containing the red nucleus) in blue, and the internal capsule in solid black. The ventrocaudal (not shown) thalamic nucleus (not shown) is dorsal and posterior to the STN. The brachium conjunctivum is just medial and slightly posterior to the STN, and the internal capsule is lateral and ventral. Also shown are the nerve fibers exiting the oculomotor nucleus to form the third cranial nerve. The DBS lead in this case is too ventral, causing activation of the internal capsule and tonic muscle contraction when the most ventral contact is used as the negative contact. One response would be to move the electrical field dorsally, away from the internal capsule. (Adapted from Schaltenbrand and Wahren, 1977.)*

see Figure 6.9). Sometimes, if the DBS lead is too ventral and every electrode configuration continues to result in tonic muscle contraction, the lead can be moved dorsally with surgery performed under local anesthetic and fluoroscopic control. Surgery should be done with the stimulator on to monitor side effects and efficacy.

DBS Lead Too Lateral

Tonic contraction can also occur if the DBS lead is too lateral (Figure 7.4). To prevent these muscle contractions, stimulation should be administered through the more dorsal leads. You would typically start with monopolar stimulation and then progress to wide bipolar and to narrow bipolar stimulation, as necessary. However, such approaches may be limited because the most effective stimulation site may be more ventral. If these measures fail and efficacy is insufficient, another approach would be to use multiple cathodes in an interleaved manner such that a lower stimulation current/voltage is applied to the more ventral contact (note that this

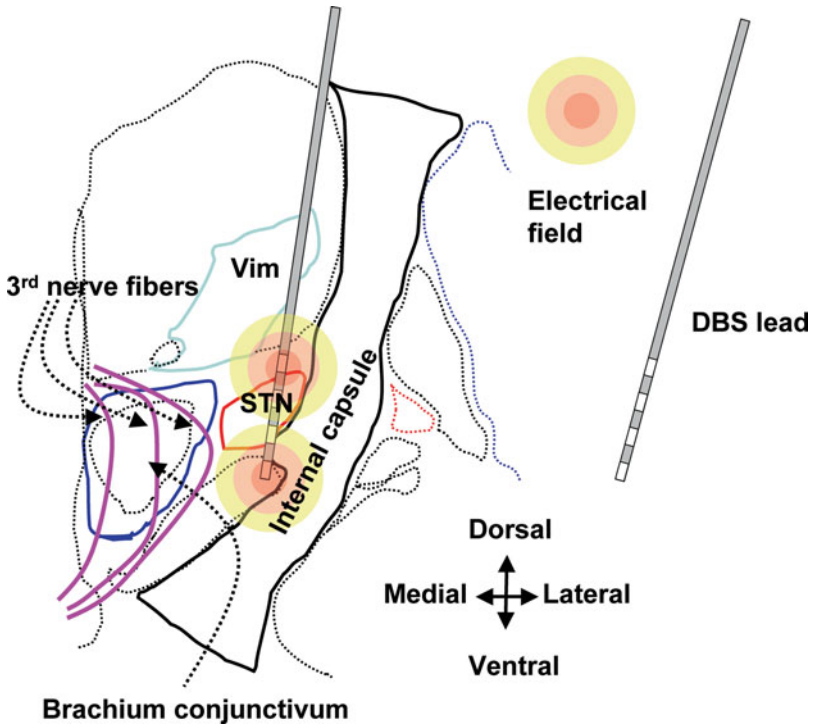


FIGURE 7.4. *Coronal view of the STN 4 mm anterior to the midpoint of the line connecting the anterior and posterior commissure (AC–PC line). The STN is outlined in red, the ventrointermediate nucleus of the thalamus (Vim) in green, the brachium conjunctivum (also containing the red nucleus) in blue, and the internal capsule in solid black. The ventrocaudal thalamic nucleus (not shown) is dorsal and posterior to the STN. The brachium conjunctivum is just medial and slightly posterior to the STN, and the internal capsule is lateral and ventral. Also shown are the nerve fibers exiting the oculomotor nucleus to form the third cranial nerve. The DBS lead in this case is too lateral, causing activation of the internal capsule and tonic muscle contraction when the most ventral contact is used as the negative contact. Evidence of the DBS lead being too lateral is that the threshold to tonic muscle contraction might be higher with the most dorsal contact as the negative contact compared to the threshold when the most ventral contact is used as the negative contact. One response would be to move the electrical field more dorsal away from the internal capsule. (Adapted from Schaltenbrand and Wahren, 1977.)*

does not necessarily mean the most ventral contact; see Figure 6.9) and a greater stimulation current/voltage is applied to more dorsal contacts (note that this does not necessarily mean the most dorsal contact; see Figure 6.9).

DBS Lead Too Posterior

The ascending fibers of the medial lemniscus and spinothalamic pathways run posterior to the STN. If the DBS lead is too posterior, stimulating the medial lemniscus and spinothalamic pathways, it can produce paresthesias (Figure 7.5). *Transient* paresthesias are not a problem; however, *persistent* paresthesias are. The most effective way to prevent paresthesias when the DBS lead is too posterior is to use bipolar configurations, beginning with wide bipolar stimulation and progressing to narrow bipolar stimulation as necessary. Alternatively, you can stimulate through the more dorsal contacts because the lead is typically anterior to posterior in the sagittal

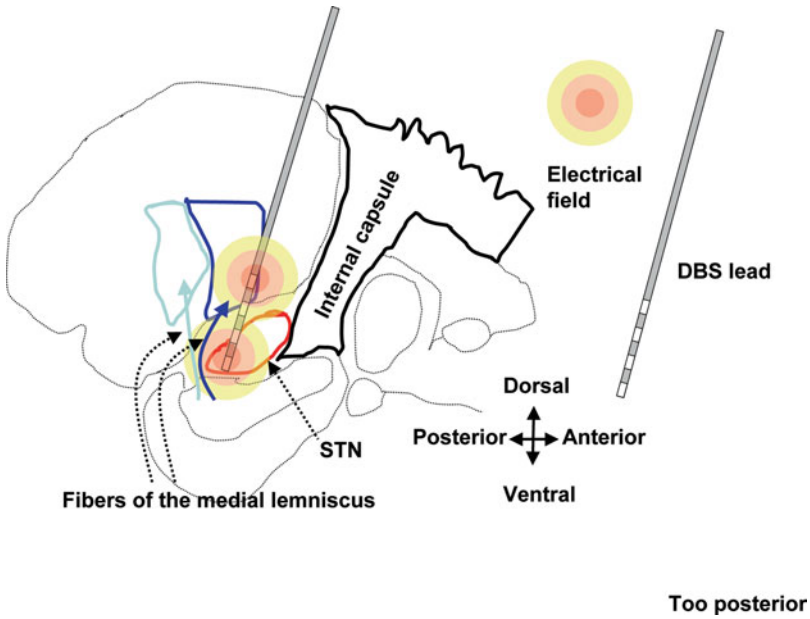


FIGURE 7.5. *A sagittal section 16 mm lateral to the AC–PC line showing the STN (outlined in red) with a DBS lead that is too posterior. Electrical stimulation spreads to the fibers of the medial lemniscus, causing paresthesias. One way to prevent paresthesias is to move the electrical field upwards by using more dorsal contacts as the negative contact because the typical trajectory slopes from anterior to posterior as it descends. Other approaches include the use of bipolar configurations, beginning with wide bipolar and progressing to narrow bipolar stimulation, as necessary. (Adapted from Schaltenbrand and Wahren, 1977.)*

plane. Moving the electrical field dorsally also moves the field anteriorly. However, such approaches may be limited because the most effective stimulation site may be more ventral. If these measures fail and efficacy is insufficient, another approach would be to use multiple cathodes in an interleaved manner such that a lower stimulation current/voltage is applied to the more ventral contact (note that this does not necessarily mean the most ventral contact; see Figure 6.9) and a greater stimulation current/voltage is applied to more dorsal contacts (note that this does not necessarily mean the most dorsal contact; see Figure 6.9).

Patients can experience psychological side effects from STN DBS, including depression, mania, and impulse control problems. Although the exact mechanisms of these side effects are unclear, they most often occur with stimulation through the most ventral contacts. Moving the electrical field dorsally often resolves these problems.

Approach to Subthalamic Nucleus DBS for Parkinson's Disease

DBS programming has to be understood in the larger context of the entire treatment program, particularly in Parkinson's disease. Programmers have to be expert not only in DBS but also in managing medications and other treatments. Consequently, postoperative DBS management should not be undertaken by those without expertise in the total management of Parkinson's disease (see Commentary 3.1).

The primary purpose of STN DBS is to improve symptomatic control. A measure of success is the degree to which medications can be reduced. Continued dependence

on medications may indicate that DBS is not optimal. The goal of treatment is not necessarily to reduce or eliminate the concurrent use of medications (except when medications are causing marked side effect), but some programmers tend to abandon further DBS programming too quickly and resort to using medications more aggressively. However, this strategy is a poor choice because, by definition, patients would not have had DBS surgery had medications been effective.

DBS programming is complex for multiple reasons, not the least of which are the synergistic effects between DBS and anti-Parkinson medications. Some programmers arbitrarily reduce the medications when DBS is started, which may result in precipitous worsening of the patient's symptoms and places the patient at risk for complications. Instead, consider an iterative approach of first improving the patient's symptoms with DBS programming followed by reducing the medications, followed by further DBS programming, and so on until optimal symptom control is achieved. This approach takes time, patience, and commitment on the part of patients, caregivers, and programmers alike. Particularly important is the commitment to see the patient frequently enough to provide a through exploration of the programming options within a reasonable time frame. One of the most common mistakes is to quit too early.

The choice of which of the numerous anti-Parkinson medications to reduce first depends on which medication-related side effect is worse. For example, if dyskinesias are the most troublesome, then those medications most likely to cause dyskinesias are reduced first. In order of greatest to least risk of dyskinesia, these medications are (1) catecholamine-*O*-methyl transferase (COMT) inhibitors, such as entacapone or tolcapone; (2) immediate-release carbidopa–levodopa; (3) controlled-release carbidopa–levodopa; (4) the dopamine agonists, such as pramipexole and ropinirole; and (5) anticholinergics, such as benztropine and trihexyphenidyl. If cognitive or psychiatric problems are the most troublesome, then medications with the greatest risk of these complications should be reduced first. They are, in decreasing order, (1) anticholinergics; (2) pramipexole; (3) ropinirole; (4) controlled-release carbidopa–levodopa; (5) COMT inhibitors; and (6) immediate-release carbidopa–levodopa.

Because the primary purpose of STN DBS is to improve symptoms, the symptoms should be readily apparent during the programming session. Thus, patients should be asked to forego their anti-Parkinson medications overnight to allow their symptoms to surface during the programming session. However, medications need to be withheld cautiously. Patients may be highly symptomatic and at risk for complications, such as falls and the rare neuroleptic malignant-like syndrome. Ask patients how they function when they wake up in the morning. If their function is poor enough that they would be at risk, have them continue to take their medications. An alternative is to advise patients to take their first morning dose and schedule the programming session just prior to their next dose of anti-Parkinson medications. Presumably, the effects of the medications would be minimal, and any symptoms not controlled by DBS would be apparent at this time.

Due to the synergistic effects between the anti-Parkinson medications and DBS, you should assess the patient for medication interactions after the DBS programming session. Typically, patients take their medications after the programming session and, 1 hour later when the medications most likely have reached their

maximal effects, are assessed for any medication-related side effects. If side effects worsen, avoid the temptation to reduce electrical stimulation; rather, reduce the medications.

Different symptoms respond to changes in stimulation at different times. Tremor and muscle tone are affected within seconds and bradykinesia within seconds to minutes. However, postural stability and gait may take tens of minutes to change. Consequently, the initial DBS parameters are based primarily on tremor, muscle tone, bradykinesia, and side effects, but you should also observe the patient after approximately 20 minutes to assess postural stability and gait.

Some commercially available and anticipated IPGs are rechargeable. Although this has a significant advantage in reducing surgeries for IPG replacement, there are concerns regarding the consequence of IPG failure due to lack of recharge. This is particularly an issue for patients with Parkinson's disease. Many patients are able to substantially reduce their medications and consequently depend greatly on DBS for symptomatic control. This means that in the event of an IPG failure, the patient's parkinsonism could worsen dramatically and expose the patient to serious consequences.

8

Approach to the Globus Pallidus Internal Segment

Regional Anatomy of the Globus Pallidus Internal Segment

Just ventral to sensorimotor region of the globus pallidus internal segment (GPi) is the optic tract. Spread of stimulation to the optic tract can produce phosphenes (the experience of seeing light without light actually entering the eye). The internal capsule lies just posterior to the globus pallidus, and stimulation there can cause tonic muscle contractions. Anteriorly lies the nonmotor region, and stimulation of this region could cause changes in cognition and personality, although the incidence of these problems is much less than with subthalamic nucleus (STN) DBS.

Side Effects Resulting from the Position of the DBS Lead Relative to the Globus Pallidus Internal Segment

DBS Lead Too Ventral

If the DBS lead is too *ventral*, electrical current will spread to the internal capsule, causing tonic muscular contraction, and to the optic tract, causing *phosphenes* (bright flashing lights in the visual fields; Figure 8.1). The usual response is to move the electrical field dorsally, first in a monopolar configuration and subsequently in a bipolar configuration. This circumstance may be appropriate for partitioning the stimulation current/voltage among the electrode contacts. For example, stimulation through the most ventral contact is most effective in producing a clinical response but produces side effects. Stimulation through the more dorsal contact does not produce sufficient benefit but does not produce as many side effects. One could stimulate both through the most ventral contact at a reduced stimulation current/voltage and then through a more dorsal contact at a higher stimulation current/voltage. However, see Figure 3.23 for caveats in the case of IPGs that interleave the partitioned stimulation parameters. (Note that the terms *more ventral* and *more dorsal* do not necessarily mean the "most ventral" and "most dorsal" contact, respectively; see Figure 6.9). If this change fails, patients can be taken to the operating room and, under local anesthesia with continual DBS testing, the DBS lead can be pulled back under fluoroscopic control.

DBS Lead Too Posterior

If the DBS lead is too posterior, electrical current will spread to the internal capsule, causing tonic muscle contraction, as described previously (Figure 8.2). DBS through

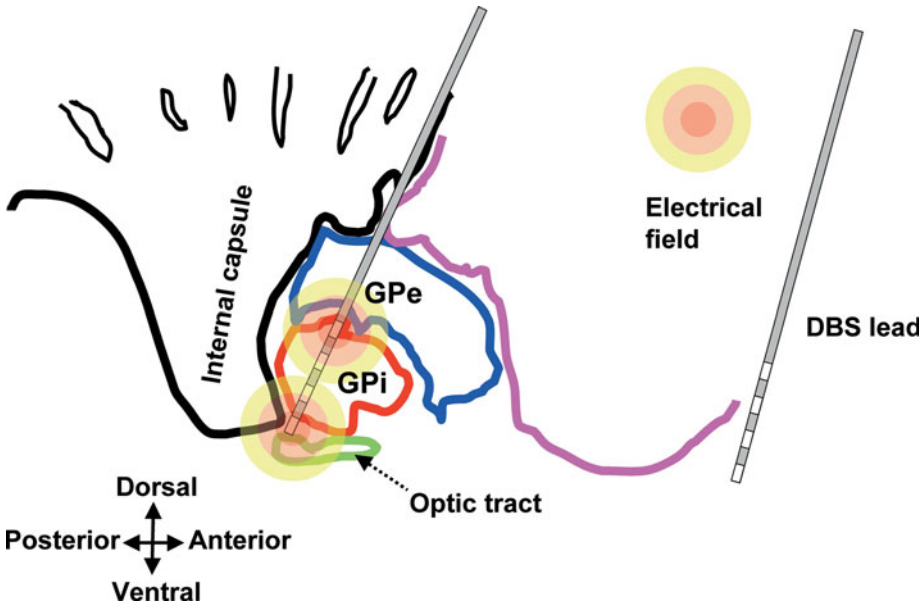


FIGURE 8.1. *A sagittal section 22 mm lateral to the AC–PC line showing the GPi (outlined in red) with a DBS lead that is too ventral. Also showing shown is the globus pallidus external segment (GPe) in blue, the optic tract in green, and the internal capsule in black. In this case, electrical stimulation spreads to the fibers of the optic tract, causing visual disturbances such as phosphenes. One way to prevent phosphenes is to move the electrical field upwards by using more dorsal contacts as the negative contact. Other approaches include the use bipolar configurations, beginning with wide bipolar and progressing to narrow bipolar stimulation, as necessary. (Adapted from Schaltenbrand and Wahren, 1977.)*

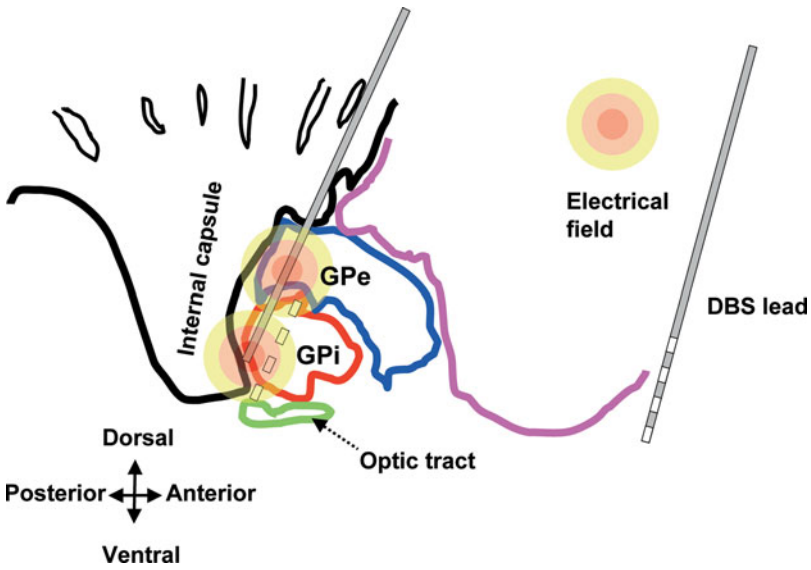


FIGURE 8.2. *A sagittal section 22 mm lateral to the AC–PC line of the GPi segment (outlined in red) with a DBS lead that is too posterior. Also shown is the GPe in blue, the optic tract in green, and the internal capsule in black. In this case, electrical stimulation spreads to the fibers of the internal capsule, causing tonic muscle contractions. One way to prevent tonic contraction is to move the electrical field upwards by using more dorsal contacts as the negative contact because the trajectory typically moves anterior with more dorsal contacts. Other approaches include the use of bipolar configurations, beginning with wide bipolar and progressing to narrow bipolar stimulation, as necessary. (Adapted from Schaltenbrand and Wahren, 1977.)*

a lead that is too posterior can result in tonic muscle contractions. Often, the DBS lead moves from anterior to posterior in the sagittal plane. For DBS leads that are too medial or too posterior, moving the electrical field more dorsally may also move the electrical field more anteriorly. However, such approaches may be limited because the most effective stimulation site may be more ventral. If these measures fail and efficacy is insufficient, another approach would be to use multiple cathodes in an interleaved manner such that a lower stimulation current/voltage is applied to the more ventral contact (note that this does not necessarily mean the most ventral contact; see Figure 6.9) and a greater stimulation current/voltage is applied to more dorsal contacts (note that this does not necessarily mean the most dorsal contact; see Figure 6.9).

When DBS leads are too anterior or too lateral, most often symptomatic benefits are lost. In these cases, large volumes of stimulation may be required to extend the field posteriorly and medially to reach the appropriate targets. Monopolar, wide bipolar, and multiple cathodes may be necessary.

Approaches to Globus Pallidus Internal Segment DBS for Parkinson's Disease

Two strategies are often applied when administering DBS to the GPi. The point of differentiation is the remarkable efficacy of GPi DBS in suppressing dyskinesia. One approach is to use GPi DBS to suppress dyskinesia, allowing more aggressive use of medications. Alternatively, one can use GPi DBS to improve the parkinsonian symptoms and, it is hoped, reduce medications, which could help reduce dyskinesia. Thus, these strategies are based on the intentions with respect to the medication use. The principal consequence is how to direct the DBS programming relative to the patient's medications.

In some patients, the primary intention of DBS is to allow for more aggressive treatment with medications. For example, patients with otherwise good symptom control may still have disabling dyskinesias and no other side effects. For these patients, the primary goal of GPi DBS could be to suppress the dyskinesia, allowing the patients to benefit from the medications. That is, medication reduction is not a goal for these patients, and GPi DBS is primarily directed at suppressing the dyskinesia directly. For other, symptomatic, patients, GPi DBS reduces dyskinesia, allowing increases in medications to treat the other symptoms.

An alternative approach is directed at decreasing the need for medications and, consequently, the DBS is directed at reducing symptoms, either because of a lack of symptomatic efficacy or because of medication-related side effects. In these patients, symptomatic improvement is the main goal, and medication reduction is the secondary goal.

For patients for whom controlling dyskinesia is a primary goal, the initial DBS programming sessions should occur when the patient is experiencing the full effect of the medications, particularly the medication-induced dyskinesias. Typically, this is approximately 1 hour after the usual medications are taken. Observation at this time allow you to assess medication effects that may be synergistic with DBS. For example, if the patient is in the medication maximum state and is having

dyskinesias, you may want to adjust the DBS to the point at which the dyskinesias are suppressed.

You should also observe the patient when the effects of medication are minimal, typically just before the next dose of anti-Parkinson medications is to be taken. The patient's condition at this time should help you determine how to adjust the medications because in the medication minimum state the primary effect may be from the DBS. This will allow you to see what the DBS is doing and then judge how to change the medications to obtain additional benefit (see Commentary 3.1).

For patients in whom symptomatic control is the primary goal, you should program the DBS parameters when the effects of medication are minimal. The approach is analogous to that described for the STN (see Chapter 7).

Different symptoms respond to changes in stimulation at different times. Initial DBS parameters should be based primarily on tremor, muscle tone, bradykinesia, and side effects, but postural stability and gait should be assessed after approximately 20 minutes.

Some commercially available and anticipated IPGs are rechargeable. Although this has a significant advantage in reducing surgeries for IPG replacement, there are concerns regarding the consequence of IPG failure due to lack of recharge. This is particularly an issue for patients with Parkinson's disease. Many patients are able to substantially reduce their medications and, consequently, depend greatly on DBS for symptomatic control. This means that in the event of an IPG failure, the patient's parkinsonism could worsen dramatically and expose the patient to serious consequences. For those patients in whom the GPi DBS is used to suppress dyskinesia, a sudden failure of the IPG could result in markedly worse dyskinesia that could pose a serious threat to health and safety.

Treating Dystonia with DBS of the Globus Pallidus Internal Segment

DBS for dystonia is complicated by the fact that although some dystonic symptoms may be affected immediately after stimulation, the maximal response may not be seen for weeks or months. For Parkinson's disease, the best approach is to begin DBS with the parameters that create the least current drain on the IPG and then increase the electrical current/voltage because the response to the DBS is relatively fast and can be assessed during the DBS programming session. However, taking this approach to dystonia is problematic. Increasing the current/voltage at intervals of several weeks takes too long to control symptoms of dystonia.

One approach is to begin with the maximum tolerated parameters that provide reasonable symptomatic control. For example, you might begin with a wide pulse width, typically approximately 120 to approximately 180 μs; a DBS rate of approximately 150 pps; a voltage near that of the IPG battery (see Chapter 6) in the case of constant-*voltage* DBS or a current whose associated voltage is near the battery voltage for the constant-*current* IPGs; and monopolar stimulation through the more ventral leads, which are more likely to be in the sensorimotor region of the GPi. These initial parameters should be modified as indicated by the patient's side effects. Observe the patient for at least 3 weeks or until the symptomatic response appears to plateau. At that point, the parameters can be changed, often by increasing the voltage or current or switching to multiple cathodes.

Some dystonia patients require high stimulation current/voltage, pulse widths, and/or frequencies (rates), which may dramatically shorten battery life. In these circumstances, a rechargeable system may be an advantage. However, the potential consequences of an IPG failure due to lack of recharge must be considered.

Medication adjustments or intramuscular botulinum toxin injections generally are not a major concern. Most medications are relatively ineffective, and lack of a response to drug therapy is a prerequisite for DBS surgery. Generally, medications are not changed until the patient has experienced therapeutic benefit from DBS.

Treating Hyperkinetic Disorders

Although DBS treatments for hyperkinetic disorders, such as Tourette's syndrome, Huntington's disease, and tardive dyskinesia, have not been approved by the Food and Drug Administration, substantial evidence supports the efficacy of GPi DBS for these conditions (Montgomery, 2004b). The multitude of hyperkinetic disorders responding to DBS is a strong argument to consider DBS as a symptom-specific therapy rather than a disease-specific one. The implications are substantial. Typically, clinical trials are not conducted for each and every conceivable cause of pain, with the presumption that pain relief medications are relevant to the symptoms, regardless of cause. Extending that logic to hyperkinetic disorders would mean that clinical trials of every conceivable cause of hyperkinesias should not be a prerequisite to using DBS therapy. However, some caution is necessary. DBS for parkinsonism cannot currently be considered a symptomatic therapy because the same symptoms that improve in idiopathic Parkinson's disease are not improved in atypical parkinsonism. The DBS programming approach in hyperkinetic disorders is similar to the approach with GPi DBS to suppress dyskinesia in patients with levodopa-induced dyskinesia, which complicates idiopathic Parkinson's disease, as described previously.

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9 Approach to Thalamic DBS

Regional Anatomy of the Ventral Intermediate Thalamus

The ventral intermediate thalamus (Vim) is the target of therapeutic DBS. The ventrocaudal nucleus of the thalamus (Vc) lies posterior to Vim. Electrical stimulation of Vc can cause treatment-limiting paresthesias. The corticospinal and cortical bulbar tracts in the internal capsule lie lateral and ventral to Vim. Electrical stimulation of the internal capsule can cause tonic muscle contractions. There are multiple nomenclatures for the subnuclei of the thalamus. Previously, I referred to the ventrolateral thalamus (VL). Although this term is commonly used in the physiology literature, the alternative—ventral intermediate thalamus (Vim)—is used in the DBS literature. Technically, the VL refers to regions of the thalamus that receive inputs from both the internal segment of the globus pallidus (GPi) and also the cerebellum. Vim refers to the cerebellar-receiving area of the thalamus and is thus a subdivision of what is otherwise referred to as the VL. ViM is the target of DBS for tremor-related disorders addressed here. (Note that other thalamic subnuclei have been targeted for DBS in other conditions, such as Tourette's syndrome, epilepsy, and minimally conscious state patients.)

Side Effects Resulting from the Position of the DBS Lead Relative to the Ventral Intermediate Thalamus

DBS Lead Too Posterior

If the thalamic lead is placed too posterior, electrical current can affect Vc and produce intolerable paresthesias (Figure 9.1). Although transient paresthesias are not problematic, persistent paresthesias are. Moving the electrical field dorsally by using more dorsal electrical contacts as cathodes may reduce these paresthesias. This maneuver is frequently effective because the lead often has an anterior-to-posterior orientation in the sagittal plane (see Figure 9.1). Thus, moving the electrical field dorsally has the effect of moving the DBS lead anteriorly. However, this maneuver depends on the lead being in the sagittal plane. Such approaches may be limited because the most effective stimulation site may be more ventral, particularly if the angle of the DBS lead relative to the regional anatomy is too shallow. If these measures fail and the efficacy is insufficient, another approach would be to use multiple cathodes in an interleaved manner such that a lower stimulation current/voltage is applied to the more ventral contact (note that this does not necessarily mean the "most ventral" contact; see Figure 6.9) and a greater stimulation current/voltage is applied to more dorsal contacts (note that this does not necessarily mean the "most dorsal" contact;

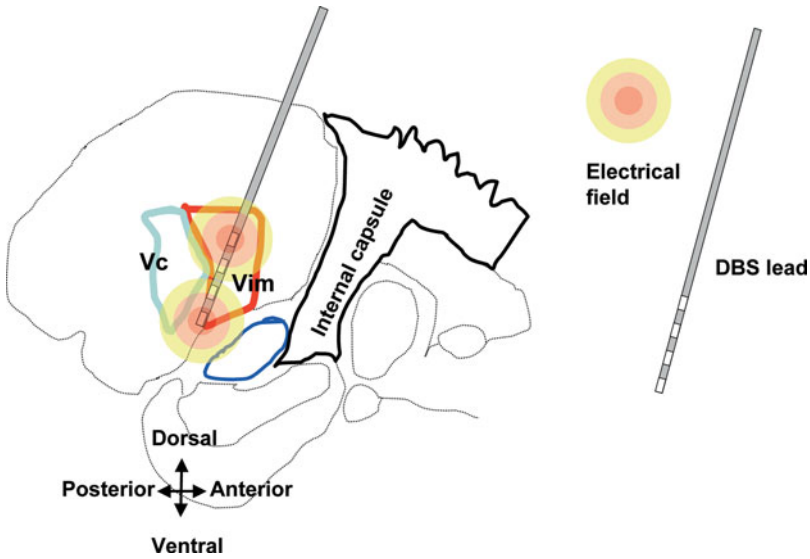

FIGURE 9.1. *A sagittal section 16 mm lateral showing the AC–PC line of the Vim (outlined in red) with a DBS lead that is too posterior. Electrical stimulation spreads to the ventrocaudal nucleus of the thalamus (Vc), causing paresthesias. One way to prevent paresthesias is to move the electrical field upwards by using more dorsal contacts as the negative contact because the typical trajectory slopes from anterior to posterior as it descends. Other approaches include the use of bipolar configurations, beginning with wide bipolar and progressing to narrow bipolar stimulation, as necessary. (Adapted from Schaltenbrand and Wahren, 1977.)*

see Figure 6.9). Another approach is to use progressively narrower bipolar active contact configurations.

Poor Orientation of the DBS Lead

If its angle is too great with respect to the vertical, the position of the lead may be such that one or none of the cathodes are actually in the cerebellar receiving area Vim, whereas the rest of the contacts may be too deep in Vc or too shallow in the basal ganglia-receiving area of the thalamus [ventral pars oralis posterior (Vop)] (Figure 9.2). Contacts more ventral to Vim may be in Vc, where stimulation may cause paresthesias, and the more dorsal contacts may be in Vop, which is the pallidal receiving area where DBS may be less effective. Consequently, the surgeon should attempt to place the DBS lead as vertically as possible. DBS leads that are too shallow often have to be replaced.

DBS Lead Too Lateral

The internal capsule borders Vim on the lateral and ventral sides. Stimulating the internal capsule can produce contralateral tonic muscle contractions. The monopolar survey can help determine whether the DBS lead is too deep or too lateral (Figure 9.3). For a lead that is too lateral, the threshold to tonic contraction through the most dorsal cathode is similar to the threshold through the most ventral cathode because the lead is often more parallel to the internal capsule anteriorly. The most effective way to prevent muscle contractions when the DBS lead is too lateral is to use

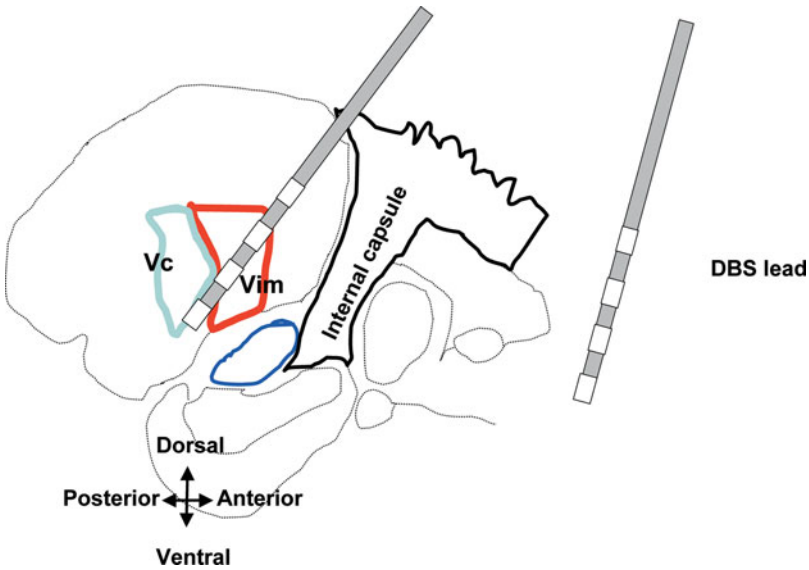

FIGURE 9.2. *A sagittal section 16 mm lateral showing the AC–PC line of the Vim (outlined in red) with a DBS lead that is angled too shallow. This results in the most ventral and ventral contact in or near the ventrocaudal nucleus of the thalamus (Vc), where electrical causes paresthesias. The dorsal and most dorsal contacts are not optimally in Vim, resulting in poor clinical efficacy. Often, DBS leads in this position have to be replaced. (Adapted from Schaltenbrand and Wahren, 1977.)*

bipolar configurations, beginning with wide bipolar and progressing to narrow bipolar stimulation as necessary.

DBS Lead Too Ventral

If the DBS lead is placed too deep or ventral, the threshold for tonic muscle contraction will be less with the ventral active contacts than with the more dorsal contacts (Figure 9.4). To prevent muscle contractions when the DBS lead is too ventral, stimulation should be done through the more dorsal leads. You can start with monopolar stimulation and then progress to wide bipolar and narrow bipolar stimulation as necessary. This circumstance may be appropriate for partitioning the stimulation current/voltage among the electrode contacts. For example, stimulation through the most ventral contact is most effective in producing a clinical response but produces side effects. Stimulation through the more dorsal contact does not produce sufficient benefit but also does not produce as many side effects. One could stimulate both through the most ventral contact at a reduced stimulation current/voltage and then through a more dorsal contact at a higher stimulation current/voltage. However, see Figure 3.23 for caveats in the case of IPGs that interleave the partitioned stimulation parameters. (Note that the terms *more ventral* and *more dorsal* do not necessarily mean the "most ventral" contact or "most dorsal" contact, respectively; see Figure 6.9). If the DBS lead is too ventral and every electrode configuration continues to result in tonic muscle contraction, the DBS lead can be moved more dorsally with surgery performed under local anesthetic and fluoroscopic control. The patient should be stimulated during surgery to monitor side effects and efficacy of the new placement.

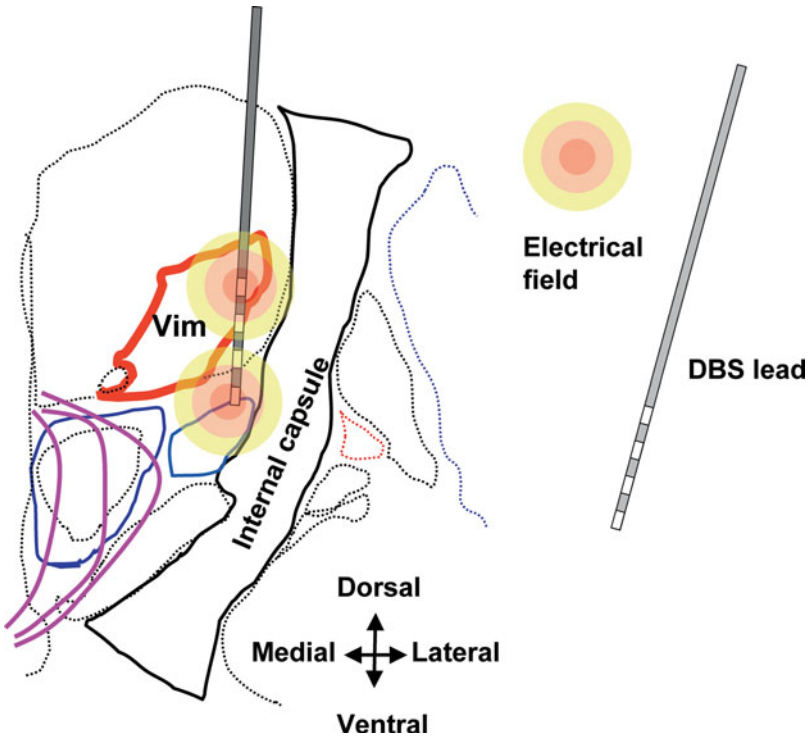

FIGURE 9.3. *A coronal section 4 mm anterior to the midpoint of the AC–PC line of the Vim (outlined in red) with a DBS lead that is too lateral. Electrical stimulation spreads to the internal capsule (outlined in black), causing muscle contractions. The internal capsule is closer to the most ventral contact, and it is less than the distance between the most dorsal contact and the internal capsule. This difference means that the threshold for muscle contraction will be less for monopolar stimulation through the most dorsal compared to stimulation through the most ventral contacts. The most effective way to prevent muscle contractions when the DBS lead is too lateral is to move the electrical field higher or to use bipolar configurations, beginning with wide bipolar and progressing to narrow bipolar stimulation as necessary. (Adapted from Schaltenbrand and Wahren, 1977.)*

Effects of DBS on Speech and Swallowing

Speech problems sometimes occur in patients receiving thalamic DBS. Consequently, a relative exclusion criterion for thalamic DBS is a marked, preexisting speech or swallowing problem. The mechanisms by which thalamic DBS affects speech and swallowing are unknown. Problems can occur in patients without other DBS side effects, suggesting that DBS can affect speech and swallowing without directly affecting Vc or the internal capsule. The general presumption is that placing the thalamic DBS in the head homuncular representation in Vim (more medial) is more likely to cause these problems.

Often there is no programming method to reduce speech and swallowing complications without simultaneously reducing therapeutic benefit. Consequently, some centers routinely use IPGs that allow the patient or caregiver to adjust the stimulation voltage or current. Thus, when speech or swallowing control is relatively more important than suppressing tremor, the patient or caregiver can set the IPG to a lower voltage or current. Conversely, when tremor control is relatively more important, the IPG can be set to a higher voltage or current. Note that some devices for patient and/or caregiver control of the

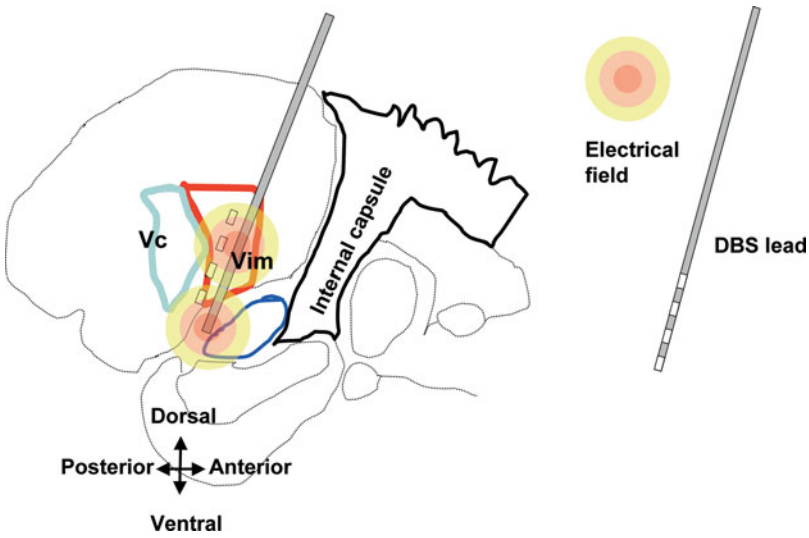

FIGURE 9.4. *A sagittal section 16 mm lateral showing the AC–PC line of the Vim (outlined in red) with a DBS lead that is too ventral. The ventral contacts are too close to the internal capsule such that stimulation through these contacts causes tonic contraction, which may be prevented by moving the electrical field higher. (Adapted from Schaltenbrand and Wahren, 1977.)*

stimulation parameters do not provide feedback to the patient and/or caregiver; consequently, patients and/or caregivers can become confused about the current status of the stimulation parameters. Other IPGs allow patients and/or caregivers to switch among predefined electrode configurations and stimulation parameters, thereby reducing ambiguity. In some commercial stimulators, the device given to patients or caregiver to increase the stimulation voltage (or any other parameter) provides no warning if the stimulation voltage exceeds safe levels. Consequently, you should limit the upper limits of the stimulation parameters, such as voltage, to keep stimulation within safe levels. Again, it is important to recognize that some commercial IPGs make certain assumptions about therapeutic impedance when calculating the electrical current densities (see Chapter 4). You should consult the appropriate manufacturer's manuals for information on other IPGs.

An Approach to Thalamic DBS for Tremor

Currently, the primary goal of thalamic DBS is to control tremor. Tremors respond rapidly to changes in DBS stimulation, so you can make small, incremental changes. Begin at the lowest parameters that generally improve symptoms—for example, a pulse width of 60 or 90 μs, monopolar cathodes, and a stimulation rate of 130 pps. If the patient is taking antitremor medications, begin programming when drug effects are minimal, usually after an overnight break or just before the next dose is due. You can ask the patient to postpone taking selected medications until just before DBS programming. However, use this approach with caution. If the patient's symptoms are intolerable or present a safety risk if the medications are not taken as prescribed, advise the patient to continue to take them without interruption and then observe the patient in the clinic as the time for his or her next dose approaches. This

approach is especially useful for patients with Parkinson's disease. After changing the stimulation parameters, it is also important to observe the patient for approximately 1 hour after antitremor medications are taken.

The Food and Drug Administration (FDA)-approved indications for thalamic DBS are idiopathic Parkinson's disease and essential tremor, but only unilateral DBS has FDA approval. However, bilateral thalamic DBS is often necessary to control axial tremor, particularly head tremor. Some patients benefit greatly when bilateral tremor is controlled. In such cases, bilateral thalamic DBS would be considered "off-label" and not experimental or investigational. Thalamic DBS is effective in treating cerebellar outflow tremor, regardless of the underlying cause, such as multiple sclerosis or trauma. However, acceptance of these off-label indications has been problematic and has been compounded by confusion regarding what constitutes acceptable outcomes in clinical trials and case reports (Montgomery, 2008a).

10 Helpful Programming Hints

With constant-*voltage* IPGs, wait at least 2 weeks after lead implantation before programming the IPG. Starting DBS too soon after implantation can cause marked side effects. The relative trauma of implantation can change tissue impedance. For example, if tissue impedance is high immediately after implantation, the patient will require—and will tolerate—higher electrical currents. However, as the initial tissue reaction subsides, impedance may drop and the charge density may increase, possibly resulting in side effects. Consequently, it is better to postpone programming until tissue reactions have subsided. These changes in tissue impedance may not be a factor when using constant-*current* IPGs, particularly acutely following DBS lead implantation. Programming of constant-*current* IPGs can begin as soon as convenient.

Constant-*current* IPGs have a significant advantage over constant-*voltage* IPGs because have minimal strength of stimulation is the same regardless of changes in the electrode impedances. Even in patients who have had the DBS leads implanted for some time and have minimal variation in electrode impedences, constant-*current* DBS is still advantageous for three reasons. First, each electrode may have different impedances and, consequently, the same constant-*voltage* applied to a new contact could result in very different electrical current densities and hence clinical response. Second, due to considerable intersubject variability in impedances, it is very difficult to generalize one's experience in one patient to predictions of how another patient would respond. This makes learning from experience using constant-*voltage* DBS highly problematic. Third, the stimulus pulse waveforms are full square-wave pulses due to capacitance at the electrode-brain interface (see Chapter 2).

Conduct a Monopolar Survey

The efficacy and, more important, the tolerability of DBS are directly related to the regional anatomy around the active DBS cathodes. Every patient's regional anatomy might be different. The monopolar survey can provide a reasonable representation of the regional anatomy unique to each patient. The patient's responses to the monopolar survey also provide important clues as to which electrode configurations will be most effective and least likely to cause side effects. Not every programmer conducts monopolar surveys, but in my experience, the survey often makes subsequent programming more efficient.

The stimulation parameters used during the monopolar survey are designed to activate the surrounding neural elements. Typically, in available IPG systems the DBS frequency is 130 pps, the pulse width is 90 μs, and the voltage for constant-*voltage* IPGs starts at 1 V and is increased in 0.5-V increments. For constant-*current*

IPGs, both available and anticipated, you should check the manufacturer's information. The current/voltage are increased until a response is obtained.

Always Increase the Current/Voltage to Clarify Any Side Effects

The side effects of DBS provide important clues about the anatomy around the active DBS cathodes. However, understanding these clues requires carefully assessing the nature of the side effects. For example, a patient may report having a "funny feeling" from a muscle contraction that does not visibly change the muscle's shape or action. This funny feeling can be confused with a paresthesia, in turn leading to incorrect inferences about the location of the lead and resulting in incorrect programming. Instead, continue to increase the current/voltage. If the initial sensation is related to subthreshold muscle contraction, the contraction will become obvious.

Check Therapeutic Impedances on IPGs

For constant-*voltage* IPGs, check the therapeutic impedances with each change in electrode configurations, particularly when using multiple active cathodes. Substantial decreases in impedance can increase electrical current densities above safety limits. Note that there have been concerns about the accuracy of measuring therapeutic impedances with certain IPGs, particularly when voltages less that 3.5 V are used. Also, some constant-*voltage* IPGs make certain assumptions about therapeutic impedances that may not be warranted, given the patient's unique circumstances (see Chapter 4). You should consult the appropriate manuals to determine stimulation safety and impedance measures.

Confirm That the Parameters under Patient Control Are within Safe Limits

Some IPGs allow the patient or caregiver to increase various DBS stimulation parameters. However, the patient's device may not warn of unsafe stimulation. This lack of warning is a particular problem with constant-*voltage* IPGs. Consequently, if you intend to allow the patient or caregiver to change any parameter, you should ascertain or test the highest limits under the patient's control to be sure that they are safe.

Systematically Document All Clinical Responses to All DBS Stimulation Parameters and Electrode Configurations

Some programmers document only the final DBS parameters and electrode configurations. This practice may seem efficient in the short term, but in the long term it may be inefficient. There are literally thousands of stimulation parameters and electrode configurations. Although relatively few combinations are typically used, some unusual combinations may be required to treat a given patient. You may think that you can determine the most effective combinations in a few programming sessions, but if optimal control is not achieved, you may not remember what combinations you tried. You may miss combinations that would be helpful or that would unnecessarily duplicate the combinations previously found to be ineffective.

Should a different programmer assume responsibility for the patient, he or she essentially has to start over again, at great cost and with delays in controlling symptoms. Thus, you should document the clinical response to each and every combination of parameters and electrode configurations you try. Examples of forms used to document the clinical response are shown in Appendix 2 and electronically at http://www.uab.edu/DBS_PrinciplesAndPractice

Always Reset Counters and Troubleshoot Inconsistent Responses

Many DBS systems can be affected by environmental electromagnetic fields. Fields interacting with the DBS leads can generate deleterious electrical current/voltages in the brain. For example, diathermy has resulted in abnormal heating of the DBS contacts, and the resulting tissue destruction has led to severe neurological impairment and even death. Electromagnetic fields can also change stimulation parameters and electrode configurations, resulting in undesired stimulation. Most commonly, in some IPGs the electromagnetic fields interact with the magnetic reed switch, turning the stimulator from "on" to "off," causing a sudden worsening or symptoms, or from "off" to "on," causing undesired side effects. In some IPGs, programmers can even disable the magnetic reed switch, and others do not contain a magnetic reed switch. In such cases, the patient or caregiver will not be able to control the IPG with a magnet.

Many sources of electromagnetic fields with the potential to affect IPGs are known, such as metal detectors and magnetic resonance imaging (MRI) scanners, but programmers continue to be surprised by patient encounters with unknown and unanticipated electromagnetic fields. Often, the only evidence of electromagnetic interference is the record of unaccounted activations recorded by the IPG. Frequent rechecking of the number of activations recorded in the IPG and having patients or caregivers frequently check to determine if the IPG is on or off and keep diaries of their activities just before they noted the IPG to be off can help identify the source of the interference.

You should also consult the manufacturer's manuals for information on possible interfering or dangerous electromagnetic fields.

Advise Patients to Take Their DBS Controlling Devices with Them to Emergency Rooms or Doctor Visits

Physicians and nurse practitioners who can program DBS systems are in short supply. This shortage may be particularly acute in areas far from where the surgery was performed. However, the shortage of programmers is most acute in emergent situations. The nearest emergency room or the physician's office may not have staff experienced in managing DBS systems. More important, many emergency rooms and physician offices do not have DBS programming devices. As a consequence, physicians may inappropriately avoid performing tests or procedures that pose no risk or can be conducted following some preparation of the DBS system. Alternatively, physicians may inappropriately perform tests or procedures that expose patients to risks.

Patients and caregivers should be instructed to take the devices needed to turn the IPGs off or on to the emergency room or doctor offices in emergencies. The emergency does not necessarily have to be neurological. For example, patients may

require radiological or surgical interventions for any number of reasons, and their evaluation and treatment can be affected by the presence of a DBS system. If the patient or caregiver has the controlling device, local medical staff can be instructed over the telephone as to how to turn the DBS system off. Importantly, the patient's controlling device may not be able to set the IPG voltages or currents to zero, which is recommended for patients exposed to strong electromagnetic fields such as MRI scans or electrocautery used in surgery. These cases require the professional DBS programmer.

Be Patient and Persistent

The response of the brain to stimulation is complex and poorly understood. Indeed, the remarkable effectiveness of DBS after failed pharmacological therapies and failed fetal cell transplantation argues for unique therapeutic mechanisms that are not yet fully understood. In addition, research into the mechanisms of DBS clearly shows that many hypothesized physiologic and pathophysiologic relationships are untenable and need to be revised. Consequently, the clinical response to DBS is often difficult to predict.

Given the very large number of possible combinations of stimulation parameters and electrode configurations, both you and your patients need to be patient and persistent during programming. A common mistake in DBS programming is to give up too soon. Consult with programmers with greater experience if necessary. You need to be sure that every option has been considered before giving up or scheduling repeat surgery.

When in Doubt, Turn the IPG Off and Wait

Experience with DBS in treating a variety of neurological and psychiatric disorders is increasing rapidly, but you will continually be confronted with novel situations or unusual presentations of more common clinical responses. This uncertainty is particularly true as new devices and new indications emerge.

One of the remarkable and unique features of DBS is its nearly immediate reversibility when stimulation is discontinued. This feature is especially useful when you are trying to determine whether an adverse experience is related to DBS. Suspending stimulation long enough to note changes in adverse events can be a useful strategy. However, do so carefully because the patient's original symptoms will probably worsen.

Troubleshooting

The majority of problems with DBS programming relate to poor placement of the DBS leads or a particular patient's unique regional anatomy around the DBS lead. Chapters 7 through 9 addressed potential solutions to these problems. This section addresses some approaches to diagnosis hardware and/or electrical problems. Again, these approaches are based on the principles covered in Chapters 2 and 3.

Hardware or electrical problems generally can result in (1) a lack of efficacy despite exhaustive attempts at DBS programming and (2) side effects. Side effects can be

caused by stimulating unintended structures but in the presence of normally functioning hardware and electronics. Alternatively, side effects can be the result of electrical malfunctions, resulting in unintended stimulation.

Lack of effect due to hardware and/or electronic causes is usually associated with a break in the electrical continuity of the system or migration of the DBS lead out of the effective target region in the brain. A wire in the extension or DBS lead may have broken. There may be a defect in the IPG. A break in the electrical continuity of the system usually manifests as high impedance and low current. This can be determined in many IPGs using the electrode impedance test. Note that the electrode impedance test is different from the therapeutic impedance test for some IPGs. The electrode impedance test conducts a check of the impedance and electrical current flowing between all possible pairs of DBS lead contacts and the IPG case. A high impedance in some systems would be greater than 2000 Ω and a low current would be less than 15 μa. However, with the increase in the number and types of different DBS systems, it is important that you check the manufacturer's manuals or consult directly with the manufacturer. Note that measuring impedances is complicated (see the discussion regarding impedances in Chapter 2). You should consult the manufacturer's recommendations about interpreting the electrode impedances and currents.

A break in electrical continuity could be the result of a wire conductor fracture or a disconnection between the DBS lead and the extension wire or between the

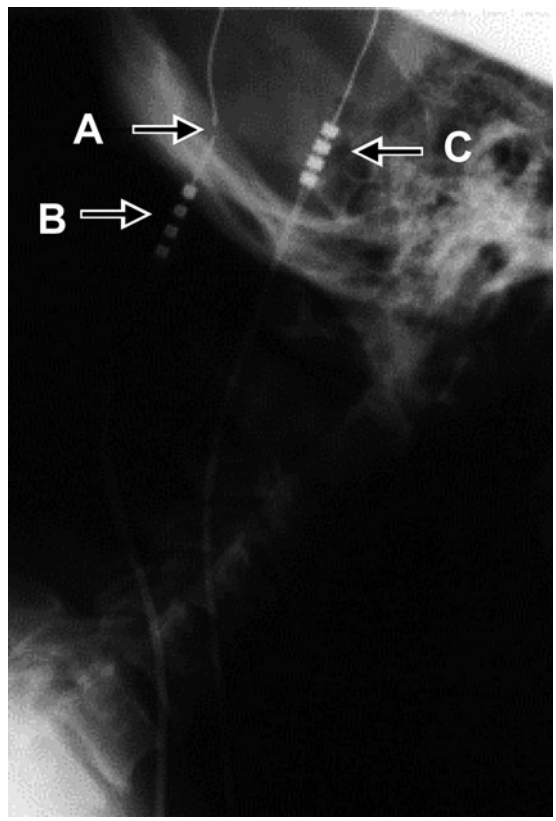

FIGURE 10.1.

X-ray demonstrating a DBS lead fracture (A). A physical discontinuity can be seen in the DBS lead. The extension connection is in the neck (B) as opposed to over the skull (C). Placing the connector in the neck and its migration from the skull to the neck are associated with a high risk of lead fracture.

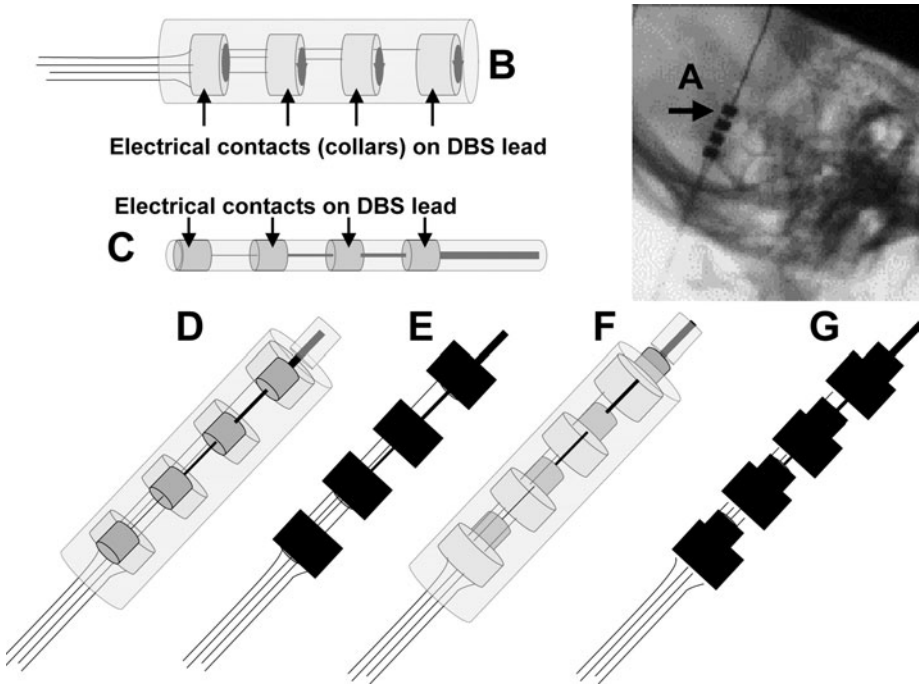

FIGURE 10.2. *Schematic representation of a normal connection and a disconnection between the DBS lead (C) and the extension (B). Figure A shows a normal connection between the DBS lead and the extension on X-ray (reverse image). The extension (B) has a series of metal collars that act to contact the electrical contacts on the DBS lead (C). If there is proper alignment (D), the electrical contacts should be inside the collars. On X-ray, the collars will be seen, whereas the electrical contacts of the DBS lead will not be seen, as shown in E and A. If the DBS lead is pulled out from proper alignment (F), then the electrical contacts will not be completely contained within the electrical collars (F) and will be seen on X-ray (G; reverse image).*

extension and the IPG. X-rays of the skull (AP and lateral), neck, and chest can be used to search for fractures or disconnections (Figures 10.1 and 10.2). I recommend obtaining these X-rays postoperatively as a matter of routine. In addition to demonstrating the physical integrity of the system and its connections, it also helps for subsequent comparisons, particularly if a lead migration is anticipated. Note that placement of the junction between the DBS lead and the extension wire in the neck increases the risk of lead fracture. Most surgeons are aware of this potential problem and place the junction over the skull. However, the junction can migrate with head movement about the neck. It is wise to periodically check the position with routine skull X-rays.

Another approach to determine whether electrical current is reaching the DBS lead is to use a small portable AM radio set to the lowest frequency. The AM radio can pick up electrical noise or interference when brought close to the DBS lead or extension. Failure to hear the electrical noise suggests that no current is flowing through the DBS lead or extension. *A note of caution*: You may need to move the AM radio around to obtain the proper orientation of the AM radio antenna to the DBS system. You should perfect your technique on a DBS system that you know is working.

Positive side effects associated with a DBS hardware and/or electrical failure usually relate to a short circuit. Also, the positive symptoms, usually manifesting as

paresthesias, can be frustratingly intermittent. Sometimes, the problems are head position-dependent. Occasionally, asking the patient to position his or her head in various positions can reproduce the symptoms. Sometimes, gentle palpation of the DBS IPG, extension wire, extension wire/DBS lead junction, or DBS lead can reproduce the positive symptoms.

These positive symptoms are often associated with multiple breaks in the extension or DBS lead allowing the exposed conductor in one wire to electrically contact the broken end of another wire, causing improper stimulation. Sometimes, a short circuit may be due to electrically conductive fluid entering into the connections. A check of the electrode impedances usually reveals low impedance and a relatively high current. You should consult the manufacturer's recommendations about interpreting the electrode impedances and currents.

Some patients may have unusual sensations over the IPG site. Typically, this occurs with the IPG in monopolar configuration with the metal contact surface of the IPG electrically active. This can stimulate peripheral nerves or cause muscle contractions. Routinely, the IPG is placed with the metal contact in contact with the skin rather than the underlying tissue, particularly muscle tissue. Sometimes, the IPG can "flip," so that the metal electrical contact surface of the IPG is in electrical contact with the muscle. Monopolar stimulation with the IPG case as the positive contact could then cause muscle contractions.

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II

The Basic Unit of Information in the Brain

In this remarkable era of molecular neurobiology and neuropharmacology, it is easy to forget that the brain is basically an electrical device. The brain encodes, processes, and transmits information electronically. Neurotransmitters, and their associated synaptic vesicle and receptor systems, basically are a means of transferring information between the electrical devices known as neurons. Neurotransmitters, which are the basis for most pharmacological interventions, are just the messenger; they are not the message. To be sure, the actions of the neurotransmitters are precisely controlled in space and time, but this control most often is exerted by the electrical action potentials that arrive at the synaptic terminals. The message containing the information (or misinformation) is encoded in the sequence of action potentials.

Even neuromodulators that act over different periods function by affecting the responses to the neurotransmitters. The neurotransmitters typically induce excitatory or inhibitory electrical currents in the postsynaptic neuron. Excitation is mediated by subthreshold depolarizations of the electrical potential energy (voltage) across the neuronal membrane (see Chapter 3). Inhibition is mediated by decreases in the neuronal membrane potentials (hyperpolarization). These depolarizations and hyperpolarizations summate in the individual neuron to determine whether an action potential, the unitary bit of information in the brain, is generated (like a "1" in the binary code in electronic computers) or not (like a "0" in the binary code in electronic computers). Thus, the processing of information by an individual neuron is electronic. The actions of neurotransmitters on an individual neuron only indirectly affect information processing, and there are many other factors involved. The actions of neurotransmitters are not synonymous with brain information processing functions.

There is a conceptual predisposition to equate chemical neurotransmission with the physiological function of neurons (Valenstein, 2005). To the degree that mediation at the neurotransmitter level (e.g., replacing dopamine with doses of levodopa) reverses the symptoms of Parkinson's disease, chemical neurotransmission is, in fact, similar to physiological function. However, the remarkable success of DBS in the face of clear failure of manipulation of neurotransmission, either with pharmacological agents or with biologicals such as fetal cell transplants, to control symptoms such as bradykinesia and akinesia is strong evidence that chemical neurotransmission is not synonymous with brain function. Furthermore, the electrical effects of DBS are superior to the effects of pharmacological agents.

Critics of this conclusion note that not every symptom is directly caused by a failure of dopamine neurotransmission and, consequently, these symptoms should not be expected to respond completely. However, such an explanation does not

account for the failure of pharmacological and biological treatments for symptoms that previously responded to dopamine. Furthermore, the delayed excitation of ventral intermediate thalamus neurons after inhibition by the action potentials arriving from the internal segment of the globus pallidus (GPi) could not have been predicted by knowing that the neurotransmitter involved is GABA (Montgomery, 2006).

Neurotransmitters released at the synaptic junctions are just the messengers; they are not the message. One merely has to consider the timescale of operations to understand the difference between electrical and pharmacological effects. DBS operates on the order of milliseconds. For example, the time difference between effective DBS at 130 pps and ineffective DBS at 100 pps is 2.3 ms, which is the difference in the interstimulus pulse intervals. Pharmaceutical agents operate over minutes to hours and cannot replicate the precise timing of information in the brain.

Considerable evidence indicates that this pattern of DBS is important in its therapeutic effect (Montgomery, 2005; Montgomery and Gale, 2008); consequently, the patterns of action potentials induced by the DBS are the key to efficacy. The

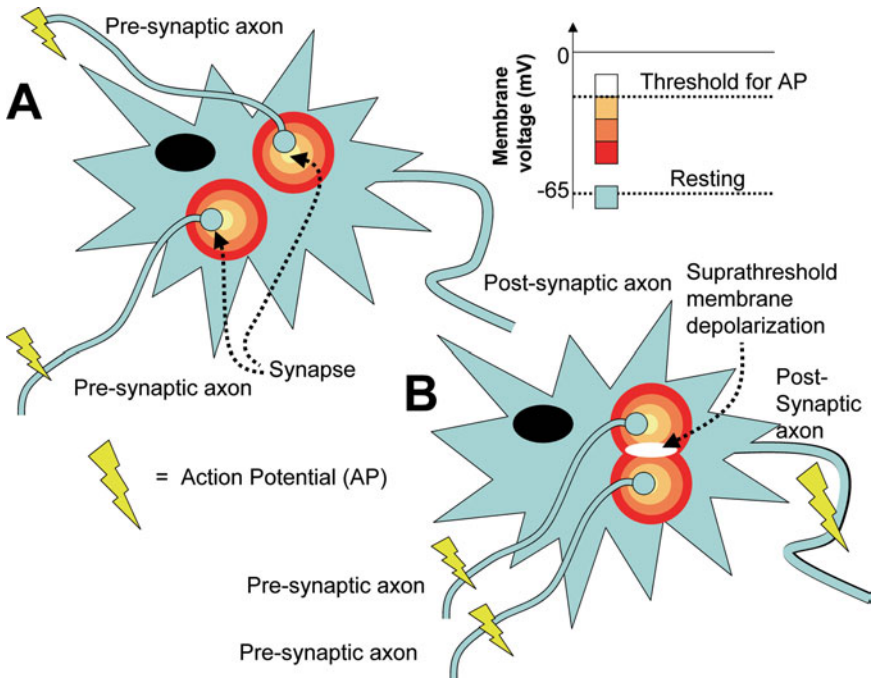

FIGURE 11.1. *Hypothetical example of the actions and integrations of electrical changes in the postsynaptic membrane associated with excitatory inputs. This figure represents two neurons. In one case (A), there are two excitatory synapses that are relatively far apart. The synaptic inputs cause a spread of depolarization (indicated by the color codes), but these do not overlap to have an adding effect. By contrast, neuron B has two excitatory synapses that are relatively close. As the depolarization from each synaptic event spreads out, they overlap. The additive effect of their overlap is sufficient to cause an action potential in the axon of neuron B. Also, spatial summation could be considered an example of Boolean logical operators. If two (or more) synapses are required to have sufficient spatial summation to generate an action potential, this would be an example of an "AND" logical operator: Input 1 and input 2 both must be true equivalent to excitatory inputs or the logical values of "1" for the output to be true, equivalent to an action potential or logical value of "1," as shown in neuron B. Reconsider neuron A. If either synaptic input was sufficient to result in an action potential, then neuron A would fire with one or both synapses depolarized the neuron. This would serve the logical operator, "OR," where if any input is true, equivalent to a sufficient excitatory input or the logical value "1," then the output is true, equivalent to an action potential or the logical value of "1." See Chapter 3 for a discussion of how changes in the neuronal membrane potential (voltage) cause action potentials.*

timescale of these patterns is very different from the time course of pharmacological or biological agents, as described previously. Information is encoded in the patterns of action potentials and information is processed by electronic integration of information encoded by action potentials, translated by neurotransmission at the synaptic junction, and then retranslated to changes in the electrical properties of the postsynaptic membrane. The changes in the neuronal electrical membrane potentials (voltages) are integrated over space and time to allow information processing. Hypothetical examples are shown in Figures 11.1 through 11.4. These examples are not based on processes that actually occur in the brain. Rather, their purpose is to attest to the computational power of neurons to integrate to electrical phenomena.

The neuronal processing resembling the logical operation of a NAND gate in Figure 11.4 is particularly interesting. The logical NAND gate holds that when two (or more) statements (inputs) are all false (and all need to be false), then the conclusion (output) is true. Any other combination results in the conclusion being false. In terms of neuronal operations, this process could mean that when a sufficient number of simultaneous inputs to the neuron are actively inhibiting, the result will be an action potential in the

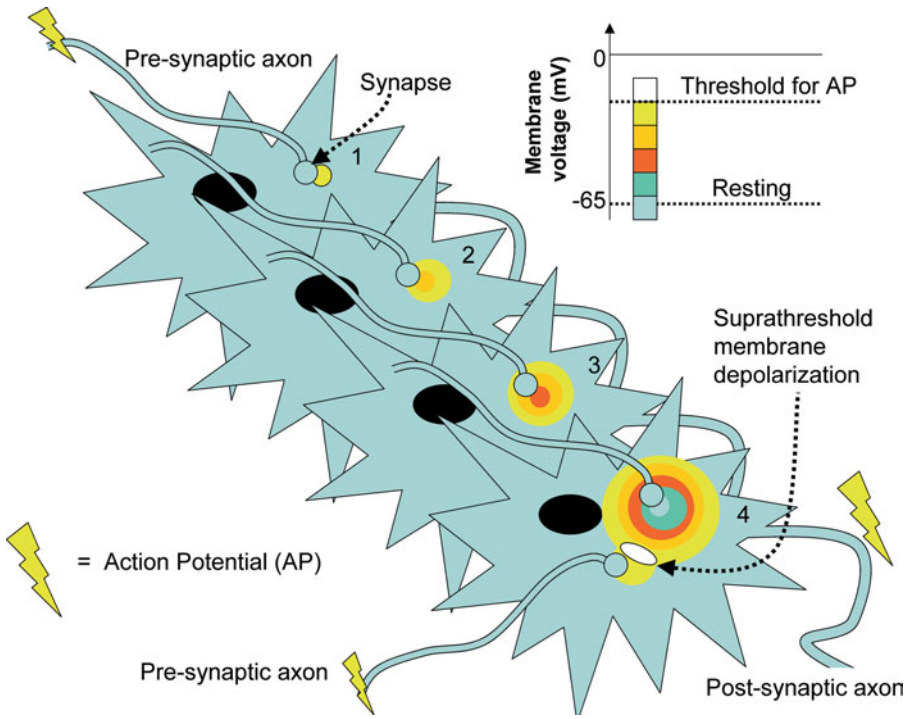

FIGURE 11.2. *Hypothetical example of temporal summation. A single neuron is represented over time (time intervals 1–4). In this case, a single excitatory input is received (time interval 1) and causes a membrane depolarization, but it is insufficient to cause an action potential. However, this change induced in the neuronal membrane voltage spreads out over time (time intervals 1–4). Later, if another synapse causes a postsynaptic excitatory potential (time interval 4), resulting in a subthreshold depolarization, this second potential by itself would not be sufficient to cause the neuron to fire and create an action potential. However, if the depolarization of the second synaptic input overlaps with the lingering subthreshold depolarization induced by the first synapse (time interval 4), the combined effect may exceed the threshold and generate an action potential. This arrangement of interactions is well suited to detecting subtle timing information in the inputs to the neuron. See Chapter 3 for a discussion of how changes in the neuronal membrane potential (voltage) cause action potentials.*

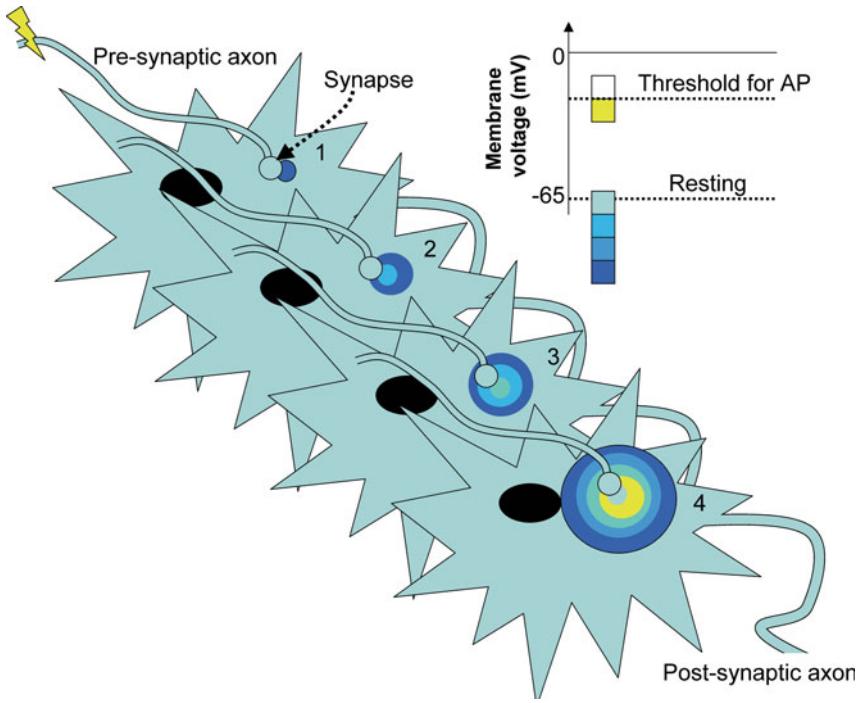

FIGURE 11.3. *Hypothetical example of a postsynaptic inhibitory input. This figure schematically represents a single neuron over time intervals 1–4. An action potential reaching the presynaptic axon terminal and releasing an inhibitory neurotransmitter changes the postsynaptic neuronal membrane potential. The neuronal membrane beneath the synapse becomes more negative (hyperpolarized). The hyperpolarization spreads over the surface of the neuronal membrane. In many neurons, hyperpolarization activates a group of ionic conductance channels (see Chapter 3 and Commentary 11.1) that cause a subsequent depolarization as seen at time 4 (the yellow circle). In this case, the depolarization is insufficient to generate an action potential. However, there are some circumstances in which it can and actually does result in an action potential. In these cases, the inhibition becomes a type of delayed excitation.*

output of the neuron. This phenomenon is seen in postinhibitory rebound excitation, which is prominent in many neurons of the basal ganglia–thalamic–cortical system. NAND gates can also be implemented in silicon transistors that make up the central processing units of digital computers. Indeed, every logical operation (which also combines to perform all mathematical operations) can be implemented as some combination of NAND gates. Thus, any computer operation basically uses various combinations of NAND gates. If the most sophisticated computers can operate on these elemental logical operations, just think of what billions of neurons, in remarkable complexities and interconnections, can achieve.

The computational power of neurons is further increased by variations in synaptic efficiencies. For example, synaptic inputs closer to the axon initial segment, where action potentials are generated, have a greater probability of initiating an action potential than do synaptic inputs far away on the dendrites. The synaptic inputs close to the axon initial segment are more likely to function as logical OR gates, whereas synaptic inputs farther out on the dendrites are likely to act as logical AND gates (see Figure 11.1).

Synaptic efficiencies can be modulated dynamically—that is, over relatively short time periods. For example, repetitive activations can *increase* the magnitude of electrical responses in the postsynaptic membrane, such as in long-term potentiation (LTP), or

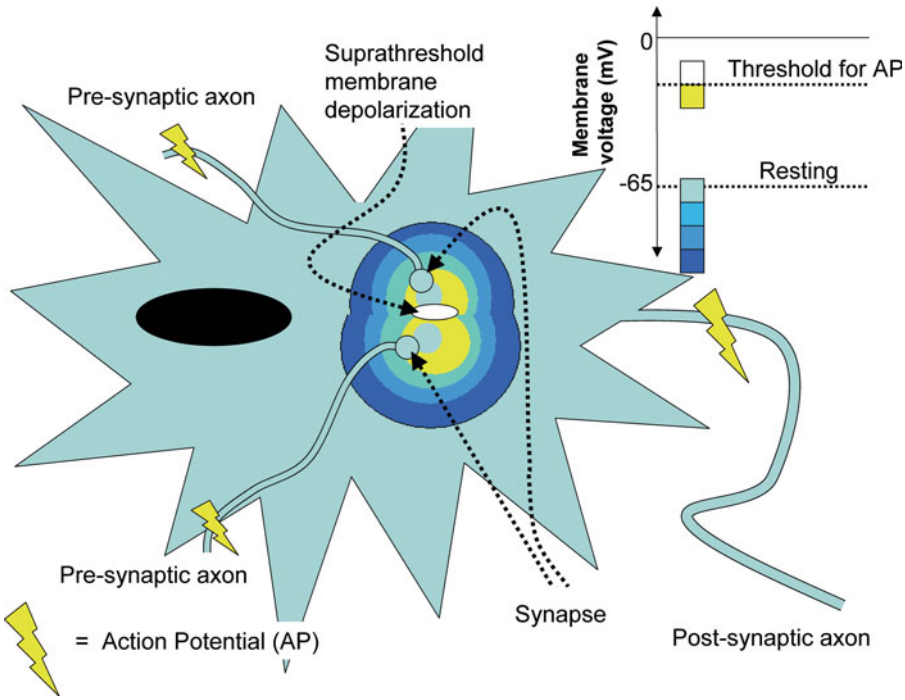

FIGURE 11.4. *Hypothetical example of spatial summation of postsynaptic inhibitory inputs and postinhibitory rebound excitation (the generation of an action potential). This figure schematically represents a hypothetical neuron that receives two inhibitory synaptic inputs at approximately the same time. Action potentials reaching the two presynaptic axon terminals release inhibitory neurotransmitters. The neuronal membrane beneath the synapse becomes more negative (hyperpolarized). The hyperpolarization spreads over the surface of the neuronal membrane. In this neuron, the hyperpolarizations summate sufficiently to activate a group of ionic conductance channels (see Chapter 3 and Commentary 11.1) that cause a subsequent depolarization sufficient to initiate an action potential. This hypothetical neuron serves as the Boolean logical operator, "NAND," in which if two inputs are false, equivalent to an inhibitory synaptic event or the logical value of "0," then the output is true, equivalent to an action potential or the logical value "1." This example is interesting because nearly every logical operation can be constructed of various combinations of NAND operations.*

decrease it, such as in long-term depression (LTD), thus constituting a form of learning. LTP can cause an excitatory input to go from subthreshold to threshold, generating an action potential. LTD can cause the converse.

The computational power based on the logical operations of individual neurons can be greatly increased with small-scale and large-scale interconnections. Indeed, the computational methods of neural networks are based on the patterns of interconnections between relatively simple operators analogous to neurons (McClelland et al., 1986; Rumelhart et al., 1986). The computational power lies in the patterns of interconnections. Neural networks can learn in a manner analogous to LTP and LTD, in which connection strengths (synaptic efficiencies) between computational units are varied. Furthermore, these neural networks can learn operations for which there is no set of instructions. For example, backing up a truck and trailer is a highly counterintuitive skill that requires considerable practice. A novice attempting this task, even with an experienced expert providing advice, would still have difficulty. Yet a network of 25 simple computationally simulated neurons can learn the task (Nguyen and Widrow, 1989).

Just as much of the computational power of a computational neural network lies in the dynamic patterns of interconnections, with varying connection strengths, so does the

computational power of the brain. Indeed, studies in nonhuman primates show that physiological functions, such as responding to a "go" signal or contracting a muscle, are not consistently represented in the behaviors of any signal neuron (Montgomery et al., 1992). Rather, a neuron's activity may be related to one physiological function in one context and to another function in a different context. The remaining candidate for the consistent representations of physiological functions is in the pattern of interconnections.

The capacity of neurons and networks of neurons to process and transmit information electronically may be the basis of the therapeutic mechanisms of action of DBS. DBS can improve information content by increasing the signal-to-noise ratio by resonant amplification or suppress misinformation (Montgomery and Gale, 2008). Understanding disorders of the brain as consequences of misinformation is a relatively new conceptualization. Traditionally, neurology categorized disorders as positive or negative symptoms or symptoms of disconnection. Positive symptoms typically were associated with excessive function, such as a seizure or spasticity. Negative symptoms were associated with a loss of function, such as paralysis or blindness. Relatively new are the disconnection syndromes in which structures that depend on each other are separated as a consequence of disease. An example is alexia without agraphia. It is hoped that in the future, neurologists and psychiatrists will come to understand brain disorders foremost as misinformation. This will result in radically different approaches to treatment.

Commentary 11.1. ***The Curious Case in Which Inhibition Is Not Inhibition***

Many current theories of basal ganglia physiology and pathophysiology rely on the assumption of inhibitory effects of the GPi on neurons of the ventrolateral thalamus. The Globus Pallidus Rate theory of basal ganglia pathophysiology posits that overactivity in the GPi causes excessive inhibition and thus decreases activity in the ventrolateral thalamic–cortical loop. Conversely, underactivity in the GPi decreases inhibition of the ventrolateral thalamic–cortical loop and consequently causes involuntary movements. The Globus Pallidus Rate theory has been generalized to normal basal ganglia physiology in the Focused Attention/Action Selection theory, in which the purpose of the GPi is to suppress unwanted movements, and inhibiting the GPi then allows the desired movements. These theories are no longer tenable (Montgomery, 2007a, 2008b). However, the one-dimensional, push–pull dynamics, such as those inherent in the hypothesized reciprocal nature of the relationship between the GPi and the ventrolateral thalamus, continue to be promoted. The modern guise of this one-dimensional, push–pull concept is a new theory positing that 20-Hz oscillators in the basal ganglia are antikinetic, whereas 70-Hz oscillators are prokinetic. Again, this new theory fails on several accounts [see Commentary 5.1 and Montgomery (2007a)].

The issue of inhibitory neurotransmission is particularly important to the basal ganglia side loops of the basal ganglia–thalamic–cortical system and to the Systems Oscillators theory of physiology and pathophysiology (Montgomery, 2004a). The Systems Oscillators theory posits the existence of several reentrant

oscillators nested in the basal ganglia–thalamic–cortical system. Continued activity within the oscillators would be necessary. However, the majority of the connections, including the connections from the GPi and substantia nigra pars reticulata to the thalamus, are inhibitory. Such a preponderance of inhibition would seem unlikely to sustain the necessary oscillations.

There are examples of oscillators made up entirely of inhibitory neurons. The crustacean stomatogastric ganglion is made up entirely of inhibitory neurons, but it retains robust oscillations of neuronal activity (Marder and Calabresi, 1996). The key to sustained oscillation is postinhibitory rebound excitation. Thus, the inhibition of a neuron, such as initiated by the release of an inhibitory neurotransmitter, is followed by excitation based on biophysical properties of the neuron. In a way, the inhibition is merely a delayed excitation, although the preceding inhibition provides several important properties, such as synchronizing activities.

Considerable evidence supports the postinhibitory rebound in the basal ganglia side loops, for example, in the subthalamic nucleus neurons. Figure 3.12 shows an example of postinhibitory rebound activation in two ventrolateral thalamic neurons in response to DBS of the GPi (Montgomery, 2006). Current theories, such as the Globus Pallidus Rate theory and the Focused Attention/Action Selection theory, do not account for the postinhibitory rebound excitation.

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12

What DBS Tells Us about Physiology and Pathophysiology

Our notions of neuronal physiology of the basal ganglia, and perhaps most systems in the brain generally, are changing. The simple hierarchical, sequential, one-dimensional dynamics that typify most current theories imply that one structure excites another structure that, in turn, inhibits the next structure. According to some accounts of basal ganglia pathophysiology, the loss of dopamine neurons in the substantia nigra pars compacta reduces the inhibitory action of dopamine on one group of the neurons in the striatum that, in turn, inhibits neurons in the globus pallidus external segment (GPe). Loss of dopamine results in disinhibition of these striatal neurons that consequently increase inhibition of the GPe neurons. Because GPe neurons inhibit the subthalamic nucleus (STN), the decrease in GPe neuronal activity decreases the inhibition of the STN, which then increases excitation of the globus pallidus internal segment (GPi), which in turn suppresses activity in the thalamic–cortical system to produce the symptoms of Parkinson's disease. Similarly, another group of striatal neurons that receive excitatory neurotransmission from dopamine neurons causes inhibition of GPi neurons. With the loss of dopamine, these striatal neurons are less able to inhibit the GPi neurons, which become overactive and suppress activity in the ventrolateral thalamic–cortical system. Thus, overactivity of the GPi is thought to be causal to the motor dysfunction of Parkinson's disease (the Globus Pallidus Rate theory). Conversely, decreased GPi activity frees ventrolateral thalamic neurons from inhibition and consequently increases their activity, generating involuntary movements such as dyskinesia. This one-dimensional "push–pull" theory of neuronal dynamics has been generalized to normal physiology, suggesting that the role of the GPi is to suppress unwanted movements and that normal movement is effected by reducing GPi activity (the Focused Attention/Action Selection theory) (Montgomery, 2007a).

DBS research clearly shows that such theories are no longer tenable (see Commentary 11.1). Studies in humans and nonhuman primates show that DBS of the STN and GPi activates or drives GPi activity (Montgomery and Gale, 2008), yet at the same time, this increased GPi activity facilitates movement in patients with Parkinson's disease rather than worsen bradykinesia, as predicted by the hierarchical–sequential theory described previously. Likewise, decreased GPi activity, which might occur with surgical ablation during pallidotomy, substantially reduces involuntary movements—a finding that, again, is contrary to the hierarchical–sequential, push–pull theories of basal ganglia pathophysiology.

A new notion of pathophysiology replaces the over- or underactivity of the GPi with the presence or absence of oscillatory activity that inhibits movement (the 20-Hz

"antikinetic" oscillations) or facilitates movement (the 70-Hz "prokinetic" oscillations). Although this new theory no longer explicitly evokes a hierarchical or sequential organization, the dynamics continue to be a one-dimensional push–pull system between the prokinetic and anti-kinetic oscillators. In the past, worsening of motor symptoms in patients with Parkinson's disease with 20-pps DBS supported the old theory; however, the fact that 20-pps DBS improves speech does not. Furthermore, 70-pps DBS in patients with Parkinson's disease is without benefit, although 70 pps would be expected to facilitate the putative 70-Hz prokinetic oscillator.

An alternative theory, the Systems Oscillators theory, posits that the basal ganglia–thalamic–cortical system is organized as sets of nested or interconnected oscillators representing many different frequencies. These different oscillators interact to greatly increase the range of oscillatory activity within the basal ganglia–thalamic–cortical system (Montgomery, 2004a). This large range of frequencies is important for the unique functions that nested oscillators are capable of performing (see Chapter 14). The oscillators are made up of nodes connected in a reentrant architecture (Figure 12.1). Activity traverses the entire circuit. The number of nodes determines the length of the circuit and the fundamental frequency of the oscillator. For example, if activity takes 4 ms to travel between nodes and there are four nodes, then the total time required for activity to make one transit around the oscillator is 16 ms, or approximately 63 Hz (= 1/0.016 s), and a two-node oscillator would have a fundamental frequency of 125 Hz.

The Systems Oscillators theory posits that the main oscillator is the reentrant circuit consisting of the thalamic–cortical system (Figure 12.2). With respect to

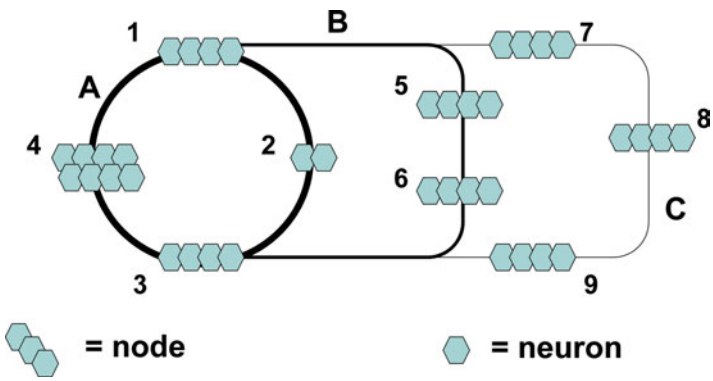

FIGURE 12.1. *A hypothetical reentrant oscillator and a set of nested reentrant oscillators. The oscillators are labeled as A, B, and C. Oscillator A contains nodes 1, 2, 3, and 4; oscillator B contains nodes 1, 5, 6, 3, and 4; and oscillator C contains nodes 1, 7, 8, 9, 3, and 4. Assuming a transmission time between nodes of 4 ms, the fundamental frequency is approximately 63 Hz for the four-node oscillator A, 50 Hz for the five-node oscillator B, and approximately 42 Hz for the six-node oscillator C. Each node contains several neurons. All but nodes 2 and 4 contain four neurons, whereas node 2 contains two neurons and node 4 contains eight neurons. According to the Systems Oscillators theory, each neuron does not discharge with each cycle of oscillation. Thus, the minimum average discharge rate of individual neurons is determined by the fundamental frequency divided by the number of neurons in each node. For neurons in node 2 of oscillator A, the minimum average discharge frequency of each neuron would be approximately 21 Hz. For neurons in node 4, when they participate in oscillator A, the average discharge frequency would be approximately 8 Hz. The theory holds that several high-frequency oscillators in the basal ganglia–thalamic–cortical system have frequencies much greater than the average discharge rate of the individual neurons within each node. The actual discharge frequencies of all the neurons are complex because the oscillators are nested. In this example, all oscillators share nodes 1 and 3. Thus, oscillations in oscillator A will spill over into oscillators B and C and vice versa. Indeed, the interactions could result in oscillations much faster than the 63-Hz fundamental frequency of oscillator A and much slower than the 42-Hz fundamental frequency of oscillator C.*

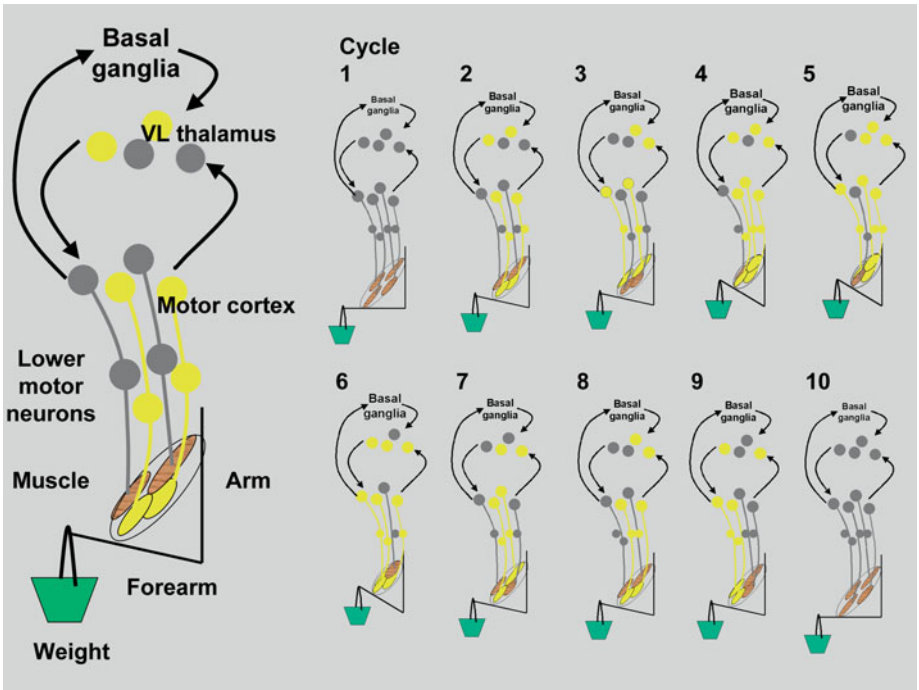

FIGURE 12.2. *Representation of the relationship of the ventrolateral thalamic–cortical oscillator to the basal ganglia and motor units in the muscle according to the Systems Oscillators theory. The figure on the left illustrates the various components. Active neurons and motor fibers are shown in yellow. The ventrolateral thalamus (VL) and motor cortex form a positive feedback loop, whereas the motor cortex projects to the motor units (a combination of lower motor neurons and muscles fibers). The activity of the motor units is sustained by ongoing reentrant activity within the VL–cortical oscillator, whereas the number of VL and motor cortical neurons active through each cycle of the oscillations is regulated by the basal ganglia (and cerebellum, not shown) side loops. The series of smaller figures represent the generation of a muscle force to elevate and lower a weight. The transition from no motor units active (cycle 1) to the beginning of the muscle contraction (cycle 2) is caused by an increase in the excitability of VL neurons in response to the influence of the basal ganglia. This influence is represented by two hypothetical neurons being activated in VL, two hypothetical neurons in the motor cortex, and two hypothetical motor units in the muscle. Likewise, the increase in motor unit recruitments (represented by three hypothetical motor units) is caused by an increase in the number of neurons active in the VL thalamus during cycle 4 that, in turn, activates three neurons in the motor cortex. The ongoing reentrant activity in the VL–cortical circuit, under the influence of the basal ganglia side loops, sustains the increased motor unit activities (cycles 2–3, 4–6, and 7–8). The process is reversed to lower the weight, again under the influence of the basal ganglia (and cerebellum, not shown).*

motor function, the main circuit is the ventrolateral thalamic–motor cortex system. This disynaptic circuit has a high fundamental frequency estimated to be approximately 143 Hz based on a 3.5ms latency between neurons. The ventrolateral thalamic–motor cortex oscillator is responsible for driving lower motor neurons and, subsequently, muscle activity. The number of motor units recruited is a function of the percentage of motor cortex neurons activated with each cycle of the ventrolateral thalamic–motor cortex oscillator. The theory also proposes that the percentage of motor cortex neurons activated with each cycle is determined by inputs from the basal ganglia (and other structures such as the cerebellum) side loops. Thus, the basal ganglia side loops determine the magnitude of motor unit recruitment and, thus, the orchestration of muscle forces necessary to produce movement (Montgomery, 2007b). Figure 12.3 depicts how the multiple side loops in the basal ganglia operate over lower frequencies to control the longer timescale of motor unit recruitment that is necessary to orchestrate the synergistic muscles to carry out a normal movement.

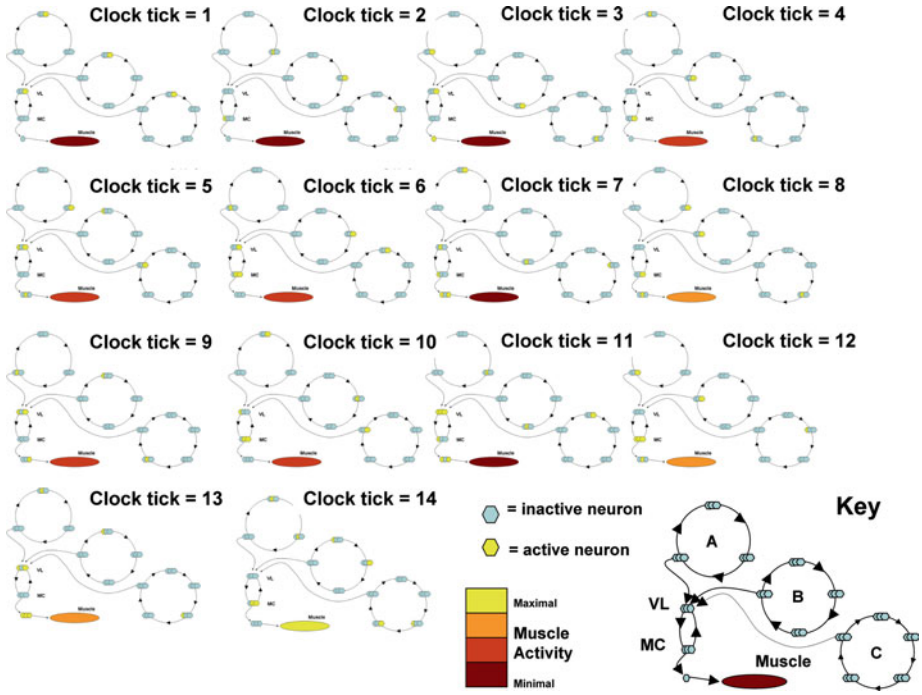

FIGURE 12.3. *Representation of the interactions between the main oscillator, the ventrolateral thalamic (VL)–motor cortex circuit, and the other side loops through the basal ganglia. Building on the concepts illustrated in Figure 12.1, the purpose of Figure 12.3 is to show how the interactions among the oscillators in the basal ganglia–thalamic–cortical system can modulate the motor unit activity over time. Three hypothetical basal ganglia side loops are represented by oscillators A, B, and C (see key). Oscillator A is a three-node loop, B is a four-node loop, and C is a five-node loop. The main oscillator, the VL–motor cortex circuit, is responsible for motor unit recruitment by the connections of the motor cortex to the bulbar and spinal motor neurons, as illustrated in Figure 12.1. The side loops determine the percentage of motor cortex neurons active with each cycle through connections from oscillators A, B, and C to VL neurons. The recruitment process begins with the activation of a single neuron in the VLs and oscillators A–C. With each clock tic, the activation from the previous node is conveyed to the subsequent node. The number of neurons activated in the subsequent node equals the number of neurons activated in the previous node during the previous clock tic. Over time, the interactions between the VL–motor cortex loop and the other oscillators gradually increase muscle force.*

The Systems Oscillators theory holds that high-frequency DBS of the thalamus, STN, and GPi (as well as direct stimulation of the motor cortex) directly activates the ventrolateral thalamic–motor cortex loop with each pulse (see Commentary 3.2). Various disease states may have a loss of signal or greater noise. In this case, the signal is the precise modulation of motor cortex excitability that precisely orchestrates the activities of motor units to drive a normal movement. High-frequency DBS may increase the excitability of the motor cortex neurons, but the frequency of the DBS must match the fundamental frequency of the ventrolateral thalamic–cortical loop.

An analogy can be made to AM radio. The AM radio station sends out an oscillating signal at a precise frequency, which is analogous to the fundamental frequency of the ventrolateral thalamic–cortical loop. The actual information is encoded in the variations in the amplitude of the electromagnetic wave that makes up the radio signal. The radio receiver receives this radio wave but also every other radio wave from any number of other radio stations. The radio receiver can isolate the specific radio station because the receiver has an oscillator that can be tuned to the exact frequency of the desired station. The oscillations in the radio receiver are the

same amplitude and thus, do not carry information, much like the DBS. However, the oscillations of the radio receiver interact selectively with the oscillating radio wave from the desired radio station to amplify that signal and not any others so that only the desired radio station is heard. Similarly, high-frequency DBS at the right frequency can amplify the original signal encoded in the motor cortex that had previously been lost in the noise as a result of disease. Improved motor unit recruitment and muscle force generation may be one mechanism by which high-frequency DBS improves bradykinesia in Parkinson's disease, at least for limb function (Montgomery, 2007b).

As suggested by the AM radio analogy, the frequencies of the DBS must match the fundamental frequencies in the targeted oscillator in the basal ganglia–thalamic–cortical system. High-frequency DBS applied primarily to the lower frequency basal ganglia side loops could have deleterious effects. In this case, the high-frequency DBS does not match the lower fundamental frequencies of the basal ganglia side loops, resulting in an abnormal pattern of neuronal activity in these loops. This abnormal neuronal activity affects the ability of the basal ganglia side loops to modulate the excitability in the ventrolateral–motor cortical oscillator necessary to orchestrate the muscle activity, which in turn is necessary for such highly complex movements as speech, gait, and balance. Lower frequency DBS, primarily in the basal ganglia side loops and particularly when it is equal to the fundamental frequencies of the side loop oscillators, has a very different effect. In this case, the pattern of neuronal activity in the basal ganglia side loop disrupted by disease could be restored. The restored patterns of neuronal activity in the basal ganglia side loops would improve the modulation of excitabilities within the ventrolateral thalamic–motor cortical loop leading to improved orchestration of motor unit activities and more normal behavior (Montgomery, 2007b).

The Systems Oscillators theory (as described in Figures 12.1 to 12.3) has several important properties (Montgomery, 2004a). Not only are the predictions of the theory consistent with empirical observations but also the theory suggests potential explanations for a range of important observations, such as the different effects of high- and low-frequency DBS on speech in patients with Parkinson's disease (see Commentary 5.1), the "U-shaped" response to increasing DBS strength (see Commentary 6.1), and the variability in latencies to response (see Chapter 13).

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13

Variability in the Latency of Responses to DBS

In a particular disease, symptomatic responses to DBS may have much different latencies. The best known example is dystonia, where it may be months before a patient improves, although other symptoms, such as phasic symptoms like tremor, will improve almost immediately to a variable degree. These long latencies are thought to be caused by adaptive anatomical changes, such as dendritic synaptic spine formation in response to constant electrical stimulation. Indeed, constant, long-term repetitive activation is a potent stimulus of dendrite spine formation. Other clinical responses in other conditions can have shorter latencies. For example, tremor and parkinsonian rigidity respond within a few seconds, bradykinesia responds within tens of seconds to minutes, and gait and balance respond in 20–30 minutes. Shorter latencies are not consistent with synaptic reorganization but, rather, are more consistent with electrophysiological changes, such as self-organization in complex nonlinear oscillators or perhaps long-term potentiation and long-term depression of synaptic transmission efficiency.

The long latencies between a change in the stimulator settings and a clinical response make treating patients with dystonia challenging. Given the huge number of potential stimulator settings, starting at some minimal setting and waiting months between each change in the setting is obviously impractical. One approach is to start at fairly high settings. For example, you might start with a larger than usual pulse width of 120 μs rather than with the more usual 90 μs. You could start with a frequency of 145 pps rather than one of 130 pps. You could also increase the DBS current/voltage until it produces side effects and then decrease the current/voltage. If there are no side effects, you could stop at a maximum of 5 V for a constant-*voltage* IPG or the milliamps recommended by the manufacturer of the anticipated constant-*current* IPGs. This last strategy provides more stimulation than necessary and, consequently, shortens battery life. However, this strategy also optimizes clinical control more rapidly.

You can program the stimulator to allow selected patients or caregivers to control the strength of stimulation with an appropriate control device. However, control devices currently on the market may not warn of stimulation currents that may exceed the safety threshold of 30μC/cm^2/phase. Consequently, you need to be sure that the maximum possible strength of patient-controlled stimulation is below this limit. Also, some commercial IPGs base their warning on certain assumptions that may or may not be valid (see Chapter 4).

The different, shorter latencies to clinical improvement for different symptoms pose interesting challenges to theories of DBS mechanisms of action. Many current

theories do not—and probably cannot—address these challenges. For example, the theory that high-frequency DBS shuts down the stimulated target through depolarization blockade, presynaptic release of neurotransmitters, or the accumulation of adenosine (Bekar et al., 2008) does not explain the variability in latencies, although it could explain their existence (Johnson et al., 2008). The theory that DBS changes abnormal discharge patterns also does not explain either the existence or the variability of these latencies.

The Systems Oscillators theory (see Chapter 12), however, can explain both the latencies and their variability. Each DBS pulse is propagated throughout the basal ganglia–thalamic–cortical system and returns to the DBS target, where the propagated effects can interact with subsequent DBS pulses. This interaction is frequency dependent, both for the DBS and for the fundamental frequency of the basal ganglia–thalamic–cortical oscillator that mediates the DBS effect (see Chapter 12). A key hypothesis of the Systems Oscillators theory is that only a small percentage of the neurons in each node of a basal ganglia–thalamic–cortical oscillator discharge with each cycle. Furthermore, DBS is inefficient at activating neuronal elements. Thus, many cycles of DBS pulses may be required to create a response sufficient to produce a clinical effect. The latency will vary depending on the frequency of the basal ganglia–thalamic–cortical oscillator that mediates the clinical effect. For example, the theory posits that motor unit recruitment is primarily the responsibility of the ventrolateral thalamus–motor cortex oscillator, which operates at high frequencies. Consequently, improving motor unit recruitment requires less time, explaining the short latencies for improved bradykinesia. However, the precise modulation of motor unit recruitment, particularly for speech, gait, and balance, requires the actions of lower frequency basal ganglia oscillators and, consequently, requires more time to reach a sufficient effect.

Systems Oscillators theory posits that a reentrant oscillation that amplifies the signal through resonance must be stimulated long enough to have a resonance effect, which translates into latencies for the effect. If different sets of oscillators underlie different functions as proposed, then the latencies needed to develop sufficient resonance effects will differ among functions, as described previously. There is evidence that DBS requires a specific duration of stimulation to create the resonance and, consequently, the therapeutic effect. Patients with Parkinson's disease were studied while undergoing three types of subthalamic nucleus (STN) DBS: continuous, moderately high-frequency DBS (approximately 90 pps); cycling DBS at 180 pps, where the stimulation was on for 0.5 s and then off for 0.5s; and cycling DBS at 180 pps, with 0.1 s on and 0.1 s off (Montgomery, 2005). Continuous and cycling DBS at 0.5 s on and off produced the same reaction times and movement velocities in a wrist flexion and extension task, and both conditions had results that were better than those of on–off cycling DBS at 0.1 s.

The same wrist flexion–extension tasks were used in another study of six patients with Parkinson's disease undergoing STN DBS. In this study, high-frequency DBS was delivered for 0.5 s every 4.5 s while the subject performed the wrist flexion–extension task asynchronously with the set of DBS pulses. Thus, the set of DBS pulses would occur once per task but at varying times during the task. For example, the set of DBS pulses could occur just after the go signal but before movement onset or after the movement was completed. The presumption was that a DBS train (a set of DBS pulses during the on cycle) given at the right time during the motor program

by the central nervous system should improve motor performance. However, reaction times and movement velocities did not differ, no matter when the set of DBS pulses was given, and these measures were both slower than those for continuous DBS (unpublished observations).

One explanation for the failure of a 500-ms duration set of DBS pulses is that a set of DBS pulses of 0.5 s is too short; however, other studies have found improvements in motor performance that were similar to those produced by continuous DBS when stimulation was on and off for 0.5 s (Montgomery, 2005). Perhaps the total number of DBS pulses delivered over a specific time is the determining variable. However, there was little or no difference in the number of pulses with cycling DBS at 0.5 or 0.1 s, although motor responses were very different (Montgomery, 2005).

The most likely explanation for the failure is that the full DBS effect takes more than 0.5 s to develop. The effects start to build over 0.5 s and last at least 0.5 s, such that delivering a set of DBS pulses of 0.5 s can reinforce the partial effect of the previous 0.5-s DBS train. This concept can be easily explained by the Systems Oscillators theory on the basis of reentrant oscillations.

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14 Oscillator Basics

Increasingly, brain physiology is thought to be based on neural oscillators (Busaki, 2006). Several kinds of oscillations can occur, some at the level of individual neurons (*neuronal oscillators*) and others consequent to interactions among neurons connected in closed feedback loops (*neural oscillators*). Neural oscillators are the main subject of this chapter. Given the increasing importance of neural oscillators, a basic understanding of them would be helpful. Thus, the following discussion is intended to provide an intuitive sense of these oscillators. Interested readers are encouraged to consult other works for more definitive and, particularly, mathematical discussions (Strogatz, 1994).

The defining feature of oscillatory activity is the recurrence or repetition of a phenomenon, such as the repetitive flashing of a light at a railroad crossing. When this type of repetitive activity recurs regularly at specific time periods, it is called *periodic*. However, not all periodic activity is necessarily oscillatory. What distinguishes oscillatory activity as a subgroup of periodic activities is the presumption that the underlying mechanism of the activity involves a repeating process. That is, periodic activities can be produced by nonrepeating processes. Imagine a line of soldiers passing by in review, saluting the review stand as they pass. The salutes would be a repeating or periodic phenomenon. However, the underlying mechanism is not repeating because each recurring salute is given by a different soldier. If the soldiers were to march in a circle in front of the reviewing stand and to salute the stand each time they approached it, then the salutes would be oscillatory: The periodic behavior is produced by a repeating process, not by a series of independent processes.

Given this intuitive notion of an oscillator, we can address how oscillators are measured, how they interact, and how they can perform important brain functions. There are many examples of physical oscillatory activity, such as the back-and-forth movement of a pendulum or race cars traversing a circular racetrack (Figure 14.1).

Oscillators can be complex, especially when they result from interactions or combinations of other oscillators. Consider the example in Figure 14.2. The back-and-forth motion, when viewed from the level of the racetrack, will be complicated and will depend on the angular velocities, or the speeds (degrees of the arc traversed per second) of the car on track A (w_A), of the rotation of track A on track B (w_B), and of the rotation of track B on track C (w_C). The path of the car depends on the diameters of track A (d_A), track B (d_B), and track C (d_C). Finally, the starting position [measured by the arc between the initial position of the race car and an arrow from the eye to the center of racetrack A (θ_A), track B (θ_B), and track C (θ_C)] must be considered. However, the complicated motion is really just the sum of the oscillations occurring on each track. The oscillatory activity on the first track (A) is summed with the oscillatory activity on the second track (B), which then is summed with the

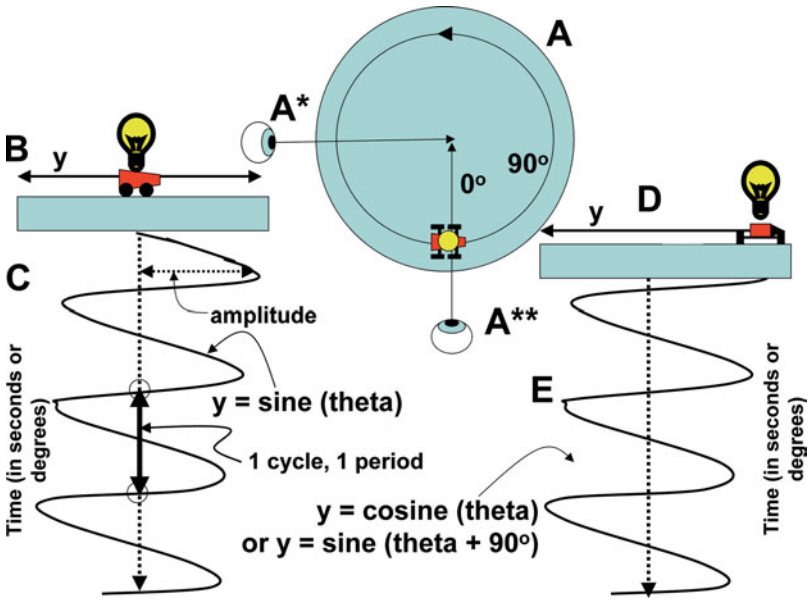

FIGURE 14.1. *An example of an oscillator represented by a race car moving on a closed circular track. A light is attached to the top of the car. The importance of the light will eventually be clear, but for the moment, the light is assumed to be constantly on. View A shows the race car and track from above, and the race car is seen as moving in a circle. The starting point can be referenced to any arbitrary point, but a point of convenience might be the line of sight from the eye to the center of the race track. Thus, two lines—the line of sight to the center of the race track and the line connecting the position of the race car to the center of the race track—create an angle, theta. The speed of the race car can be measured by its ground speed around the track, such as miles per hours. Alternatively, the speed of the race car can also be measured by the number of degrees the angle, theta, changes per unit of time (e.g., seconds). This alternative description in degrees per second is termed the* angular velocity. *When the race car circling the tract is viewed from ground level, the appearance is quite different (B and D). Now the race car is seen as moving back and forth. If we could trace the back-and-forth movement of the car over time, we would have a tracing that looks like a sine wave (C) or cosine wave (E) depending on the viewpoint. We can now define the movement of the race car as a sine or cosine function. We can also translate certain features of the sine or cosine functions to the angular descriptions when the race car is viewed from the top (A). The time it takes for the sine or cosine wave to complete both the negative and positive parts of the wave is the* period *of the wave and correlates with the time it takes the race car to make one circuit around the race track. The* frequency *is the number of complete cycles in the sine or cosine function per unit time (typically seconds) and correlates with the number of times the race car goes around the track in a unit of time. The frequency and period are related, and the frequency is the inverse of the period (frequency = 1/period). The maximum distance to the right and then to the left that the race car moves back and forth in the side view (B and D) is the* amplitude *and corresponds to the radius of the circular track when viewed from above (A). Note that the initial position of the race car is different depending on the perspectives A^{*} and A^{**}. The position of the car measured in the degrees from the original line of site is the* phase. *Note that the perspective of A^{**} in view B shows the initial position to be in the middle of the track in the line of sight. Thus, the initial phase is 0° and the subsequent tracing of the movement produces a sine wave. From perspective A^{*} in view E, the initial position is at the rightmost edge of the tract, corresponding to the maximum amplitude and with a phase of 90°, and the subsequent tracing produces a cosine wave. At the start there is a* phase difference *between the two perspectives of 90°. This phase difference is maintained as the race car circles the tract. Thus, the views from the side perspectives (B and D) maintain the same phase difference and are consequently* phase locked. *In addition, each observer would measure the same frequency and, consequently, the tow observations are* frequency coherent. *This makes sense because both observers are viewing the same car. However, it does become significant if at the beginning the observers do not know that they are observing the same mechanism.*

oscillatory activity on the third track (C), producing the plot of the location of the race car over time (Figure 14.2D). Thus, the position (y) of the race car on the horizontal plane of the racetrack at time t is given by

$$y = d_{\mathrm{A}} * \mathrm{sine}(\theta_{\mathrm{A}} + w_{\mathrm{A}} * t) + d_{\mathrm{B}} * \mathrm{sine}(\theta_{\mathrm{B}} + w_{\mathrm{B}} * t) + d_{\mathrm{C}} * \mathrm{sine}(\theta_{\mathrm{C}} + w_{\mathrm{C}} * t) \tag{14.1}$$

The term y is the position of the race car in the field of view and increases and decreases as the race car moves back and forth in the view. The term d_A*sine(θ_A + w_A*t) represents the position of the race car on track A, where d_A is the diameter of track A, θ_A is the starting point on track A measured as an angle when viewed from above, and w_A*t is the change in the position from the initial position and is determined by the product of the angular velocity, w_A, and time, t, since the observations began. The other terms for each of the other tracks can be understood similarly.

An unlimited number of racetracks can be constructed by stacking them on top of each other (see Figure 14.2). Similarly, the complexity of the movement of the race car on the horizontal plane of the racetracks in unlimited. However, no matter how complicated the movement of the race car, it can always be understood as the sum of the contributions made by all the individual racetracks. You only have to know the values of the variables: the diameter, angular velocity, and initial position (phase) of each track. However, most remarkable is the fact that all these values can be determined from the complicated path. A mathematical technique, the *Fourier transformation*, can determine the number of oscillators and their values (Strogatz, 1994). Consequently, any periodic behavior can be decomposed into a Fourier transform series similar to that shown in the following equation:

$$F(t) = d_A * \text{sine}(\theta_A(t)) + d_B * \text{sine}(\theta_B(t)) + d_C * \text{sine}(\theta_C(t)) + \ldots \quad (14.2)$$

$F(t)$ is the same as y in Eq. (14.1) except that the notion including t denotes the dependence of y over time. The sine of the various angle functions, $\theta_A(t)$, $\theta_B(t)$, $\theta_C(t)$,..., determines the amplitudes of the components of the signal $F(t)$ through time. In this case, $\theta_A(t)$ takes the place of (θ_A + w_A*t) to demonstrate the dependence of $\theta_A(t)$. This new $\theta_A(t)$ is simplified from the previous (θ_A + w_A*t) in Eq. (14.2)

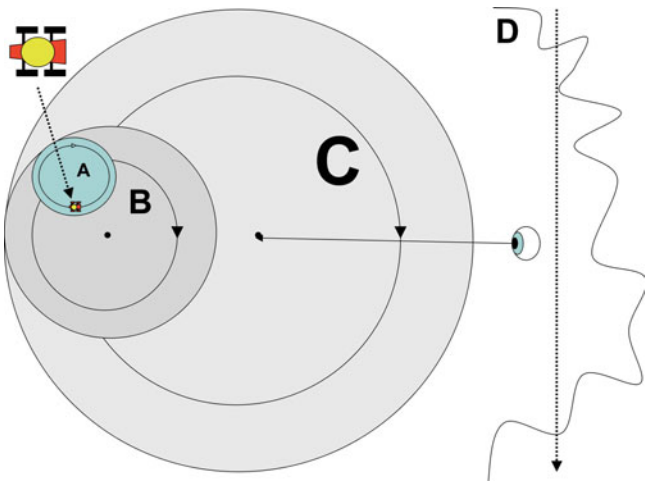

FIGURE 14.2. *In this example, the original race car track (A) shown in Figure 14.1 is itself circling another larger racetrack (B), which itself is circling an even larger racetrack (C). When viewed from the perspective represented by the schematic eye, the back-and-forth motion of the race car will be complicated (D). Tracing D is purely hypothetical and does not actually describe the back-and-forth motion of the race car; it simply shows that the motion is complicated.*

because all the initial or starting angles are the same and thereby can be dropped from consideration. The value of amplitude of the components will rise and fall from the value of "1," through "0," to "-1" and back again tracing a sinusoidal wave (see Figure 14.1*)*. The rates or speeds by which the amplitudes rise and fall, hence the frequencies, are related to the unique functions, $\theta_A(t)$, $\theta_B(t)$, $\theta_C(t)$, ... Indeed, the change in angles over time that are regular and repeating, such as $\theta_A(t)$, thus tracing a sine wave over time, can themselves be considered a frequency (see the following discussion and Eq. 14.3). The values d_A, d_B, d_C, . . . relate to the amplitude (or power) of the specific oscillator, roughly analogous to the diameters of the racetracks. Consequently, the complex movements of the race car on the horizontal surface can be considered a complex periodic function that is merely the sum of the specific regular periodic function of sine waves produced by oscillators of a single frequency weighted by the appropriate constant (d_A, d_B, d_C, . . .).

Fourier transformation is used to determine the power spectra that indicate how much power at any one frequency is represented in the complex periodic behavior. The power spectra of any complex periodic behavior are important measures of the complex behavior. Any time-varying signal, particularly repeating or periodic signals, $F(t)$, can be represented as the sum of simple frequencies f_A, f_B, f_C, with their associated magnitude constants, d_A, d_B, d_C, . . . (Eq. 14.3). Likewise, the final complex behavior can be determined from knowing the frequencies and magnitudes [and the phase of the frequencies (not shown), which varies over time]:

$$F(t) \propto d_A * f_A + d_B * f_B + d_C * f_C + \ldots \tag{14.3}$$

The concept of building complex periodic behaviors from combinations of simple oscillators of different frequencies and phases (a process called an inverse Fourier transform) is an important and powerful concept that can be applied to the complex orchestration of muscle activities that underlie movement. For example, muscle activations for rapid single-joint movements have a characteristic pattern. Initially, a burst in the agonist muscle activity is followed by a burst in the antagonist muscle and finally by a third burst in the agonist muscle. The initial agonist burst overcomes the inertial loads of the limb, and the antagonist burst brakes the initial acceleration so that the limb does not go past the target. The final agonist burst brings the limb to the target.

The actual muscle activities are caused by repetitive discharges of the lower motor neurons that, in turn, are being driven by repetitive discharges of neurons in the basal ganglia–thalamic–cortical system (and also with the input of the cerebellum, although not discussed here, but see Chapter 12). The repetitive discharges of the lower motor neurons can be thought of as reflecting the activities of an oscillator(s), like the race car on the first track. The issue then is to modulate the activity of the first oscillator(s) so as to modulate the number of motor units it recruits. This modulation can be accomplished by other oscillators. The complex pattern of muscle activity described previously (called the triphasic pattern of muscle activity for ballistic movements) can be understood as the inverse Fourier transform of the activities of the oscillators in the basal ganglia–thalamic–cortical system, as posited in the Systems Oscillators theory (Montgomery, 2008b).

The notion that patterns of increasing and decreasing muscle activity are a consequence of an inverse Fourier transformation of oscillator activities in the basal

ganglia (and, by extension, cerebellum)–thalamic–cortical systems can be extended to complex behaviors and skill acquisition. As described previously, any periodic function (within certain assumptions and limiting conditions), including any arbitrarily complex patterns of muscle activities underlying the most complex behaviors, can be decomposed by Fourier transformation into the summed or integrated activities of several oscillators. Mathematically, any arbitrarily complex function can be learned by a network of loosely coupled oscillators, provided there are enough oscillators to cover the range of frequencies in the complex function, such as the functions f_A, f_B, f_C, . . . in Eq. (14.3). Through repeated training, the "coupling strength" between certain oscillators, represented by $+d_A$, $+d_B$, $+d_C$, . . ., is strengthened and that between others weakened until trained. Then entering only the initial part of the original complex function is sufficient for the network of oscillators to produce the entire remaining portion of the complex function (Longuet-Higgins, 1968).

We can apply this concept to movement and show that neurons in the basal ganglia–thalamic–cortical system simultaneously entrain many different frequencies (Montgomery, 2004a, 2008b). Thus, the basal ganglia–thalamic–cortical system can be thought of as a set of loosely coupled oscillators. With repeated training, associations between oscillators are created by "strengthening" some and "weakening" others so that finally, when the neuronal analogue of the intent to produce a behavior is introduced into the basal ganglia (and cerebellum)–thalamic–cortical system, the coupled oscillators can produce the entire motor behavior. This initial intent need not specify the subsequent modulation of activity in the ventrolateral thalamic–motor cortical oscillator but merely trigger the completion of the signal that is specific to the necessary modulation of the ventrolateral thalamic–motor cortical oscillator. This initial intent could arise internally or be triggered by external events.

Another important implication from the modeling of loosely coupled oscillators is that the same system of oscillators can be trained to produce a variety of outputs in response to different inputs—a concept called *holographic memory* (Longuet-Higgins, 1968). Thus, the same piece of anatomy can encode multiple functions. Therefore, a precise one-to-one correspondence between a given region of the brain and a specific function is not necessary. Historically, efforts of neuroscience have been focused on establishing such one-to-one anatomical–functional correspondences (correlations) and have not always worked. The principles of holographic memory suggest that this premise of a strict one-to-one correspondence is not necessary (Montgomery, 2008b). However, the power of this long-held presumption of a one-to-one correspondence is evident in the results of a study in which nonexperts were more likely to believe a bad explanation when they were falsely told that the property was localized to a certain brain region (Weisberg et al., 2008).

The oscillators described thus far are *harmonic oscillators*, which means that their behaviors, graphed as sinusoidal functions, are continuous and everywhere differentiable, in the sense of calculus. Their behaviors are periodic and therefore predictable. However, many oscillators are not harmonic. For example, whereas the waxing and waning of a tornado-warning siren is a harmonic oscillator, the beating of a drum is a discrete oscillator; it is episodic, not continuous. In certain circumstances, a discrete oscillator may be described in the same terms as a harmonic oscillator, but

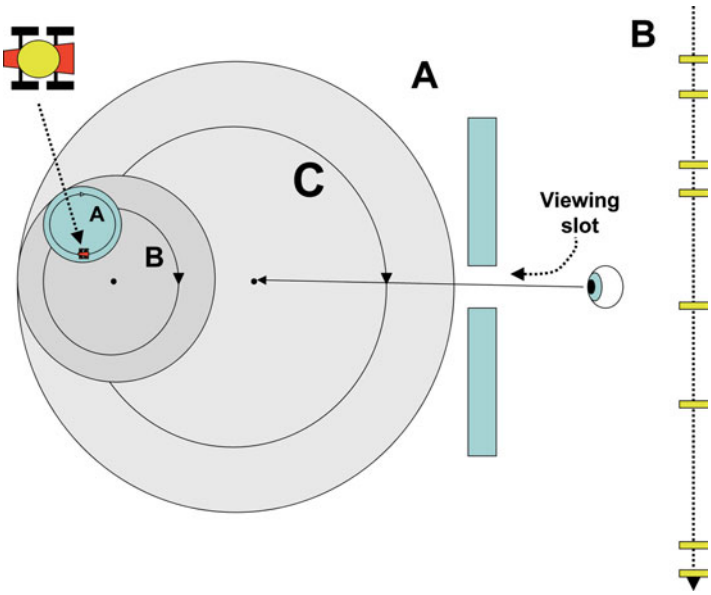

FIGURE 14.3. *An example of a discrete oscillator. The same analogy of the race car given in Figure 14.2 is used here. The car is traveling on track A, which is circling on track B, which is circling on track C. In this case, we are looking through a narrow viewing slot and see only the light as it passes in front of the slot. The result is a series of flashes over time. The series of flashes are analogous to the behavior of a discrete oscillator.*

not always. Discrete oscillators are more likely to be nonlinear (not describable in relatively simple mathematics) and, consequently, less predictable. However, the nonlinear features give these oscillators unique advantages.

One way to visualize a discrete oscillator is shown in Figure 14.3. In this case, the original race car is circling track A, which itself is circling on track B, which is circling on track C. In this case, however, we are looking through a narrow slot and see only the light on the race car as it passes the slot. The result, over time, is that we see a series of light flashes. In this case, the behavior of the discrete oscillator can be interpreted similarly to that of harmonic oscillators.

With the light continuously lit, we see a regular pattern of flashes each time the race car passes in front of the slot. Now the light flashes on and off at specific times—for example, to encode additional information. If the bulb is lit as the race car passes in front of the slot, we will see a flash of light; if not, there will be no flash. We now see a varying series of flashes. The light has a single intensity, such that it conveys only a single bit of information. However, the sequence of light flashes can encode greatly increased amounts of information, just as the sequence of "dots" and "dashes" of Morse code (Figure 14.4). The single intensity of the light flash is analogous to the "all-or-nothing" nature of the neuronal action potential and illustrates a nonlinearity in the behavior of this discrete oscillator (see Chapter 11).

The varying series of light flashes in the race car example is important from an information-content perspective. Consider the analogy of Morse code, where a sequence of dots and dashes encode the letters of the alphabet, and their order encodes the words in a sentence. A continuous and regular stream of all dots or all dashes conveys no information at all. In the race car analogy (see Figure 14.4D),

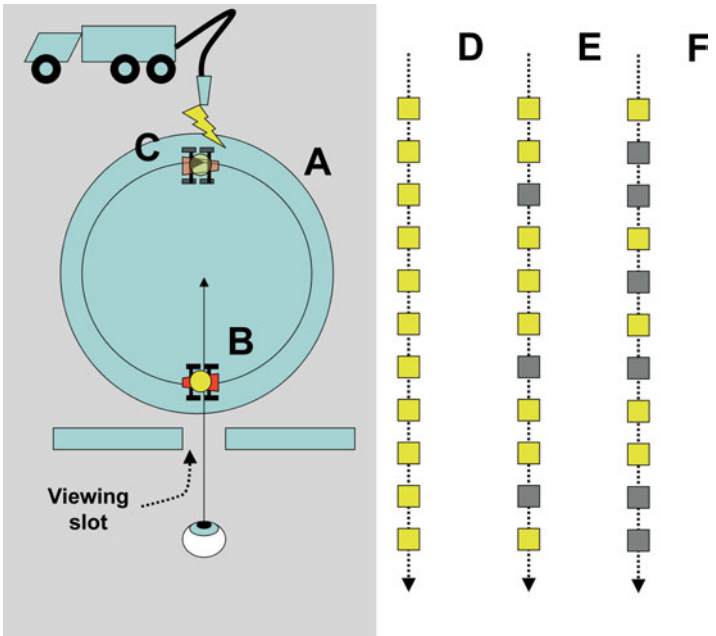

FIGURE 14.4. *An example of a more complex, discrete oscillator. The race car moving around the track produces a continuous or harmonic oscillation. However, the flashing light is a discrete process. An observer in the dark will see the light only when it is on. If the light is lit continuously, the observer will see a regular pattern of flashes as the race car passes the viewing slot (B). However, when the light is on, the race car driver cannot convey any information, except the speed the race car (D). If the driver can control when the light is on, much more information can be conveyed in the sequence of light flashes (E), a situation analogous to Morse code. A disorder of the light, such as a loose wire, may mean that it may or may not go on when the driver flips the switch. This circumstance would result in a pattern of misinformation (F). Consider the situation in which the battery that powers the light runs out of electricity. Suppose a battery charger recharges the battery each time the race car completes a cycle (C). Further suppose that the ability of the recharger to recharge the battery depends on the precise timing of the recharging process. For example, the charger can only give a recharge once per second. If the recharger has the same frequency (1 Hz) as the race car and an appropriate phase (corresponding to the position of the race car on the track), it will always be able to recharge the battery, and the driver will always be able to correctly convey information (C). In this case, the interaction between the race car and the recharger is analogous to resonance amplification. Note that if the battery charger has a different frequency from the race car or the wrong phase (timing of the recharge relative to the position of the race car on the track such that the race car is not in position to receive the charge), then there will be a failure to recharge the race car light bulb and the result will be continued misinformation.*

when the light is constantly on, the sequence of flashes contains little information (other than the frequency by which the race car circles the racetrack). On the other hand, the driver could signal the status of the race car by dimming or extinguishing the light. Now, the sequence of varying flashes visible through the slot conveys important information (see Figure 14.4E). Next, consider the circumstance in which a loose wire causes the light to go on or off when the driver does not intend it to do so. The result will be a different pattern of flashes and, consequently, different information; in the case of a loose wire, the information is misinformation (see Figure 14.4F).

This analogy has important applications in understanding DBS. As shown in Figure 14.4, a recharger on the other side of the racetrack can deliver electricity, but only in small amounts and at a certain rate. Each charge is sufficient to power the light so that it functions reliably the next time it is supposed to flash. The recharger is analogous to DBS, and each small charge is analogous to a DBS pulse. Clearly, DBS

must occur at the same frequency (and phase) so that each charge is delivered just as the car is driving past. This recharging is analogous to a resonant effect that builds (or sustains) the periodic activity of the light flashes. Now, the driver can deliver information as usual (see Figure 14.4E). One hypothesized mechanism of action of DBS is that DBS restores normal information to the nervous system (Montgomery and Gale, 2008).

The basic unit of information in the brain is the sequence of action potentials, which in the race car metaphor are analogous to the light flashes. The normal information encoded in the light flashes is analogous to the information in the sequence of dots and dashes in Morse code (see Chapter 11). Just as an abnormal sequence of dots and dashes gives rise to misinformation, an abnormal sequence of action potentials gives rise to misinformation in the brain and abnormal behaviors.

Another potential application of the analogy occurs when the electrical charge delivered by the charger (DBS) keeps the light on constantly, and the observer sees a regular series of flashes (see Figure 14.4D). The series of light flashes do not convey any information except the velocity of the race car. This would be analogous to the Morse code operator just tapping a continuous and regular series of dots. The only information is how fast the operator is typing. In this case, the information intended to be encoded in the Morse code is "overwritten" by the continuous and regular sequence of dots. This could be useful if the original signal was misinformation. In this case, the lack of information is less deleterious than receiving misinformation. Another possible mechanism of action of DBS is that the misinformation that causes the signs and symptoms of a disease is overwritten and erased by noninformation (Montgomery and Baker, 2000), a sort of "information ablation" (Grill et al., 2004) (see Chapter 15).

The complexity of the discrete oscillators described previously can be increased again. The light can still flash, but only for a very brief time, and once the light is turned off it cannot be turned on again for a brief time. This behavior of the light introduces considerable nonlinearities in the discrete oscillator. These nonlinearities arise because the behavior of the light is not continuous and therefore not predictable in the ordinary sense. The analogy to neurons is the action potential (light on) and the refractory period (light off). These nonlinearities have important implications for information processing in the nested oscillators of the basal ganglia–thalamic–cortical system. For example, suppose the driver turned the light on slightly early, before reaching the viewing slot. Now the driver reaches the slot but cannot turn the light on because it is in its refractory period. In the example with the recharger, if the driver accidentally turns the light on just before reaching the recharger, the light will again be in its refractory period and cannot be recharged.

These nonlinearities can have profound impacts on the functioning of coupled oscillators. For example, they can allow interconnected oscillators to maintain independent oscillatory activity (Figure 14.5). This property is very important so that the different oscillators in the basal ganglia–thalamic–cortical system can maintain their fundamental and different frequencies. As discussed previously, a range of different frequencies are needed to combine in an inverse Fourier transform-like process to create complex behaviors. Signals can be amplified within oscillators (Figure 14.6). Such amplification could occur in the basal ganglia side loops, which then modulate the excitability within the ventrolateral thalamic–cortical loops to

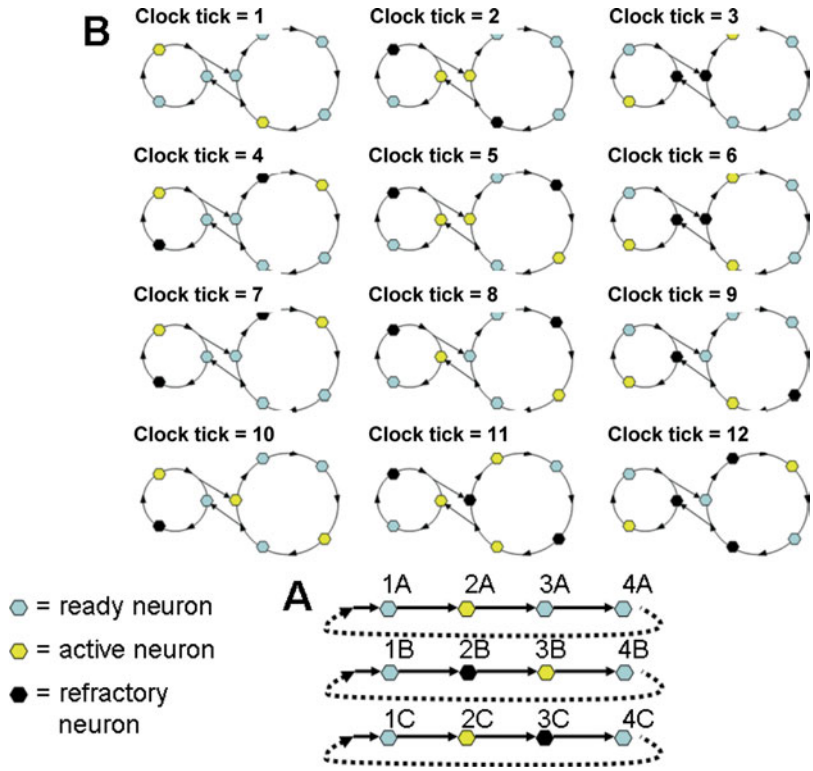

FIGURE 14.5. *An example of interactions among oscillators and the nonlinearities induced by the action potential refractory period. In the basic mechanism (A), a neuron must be ready to discharge before it can respond to a discharge from the previous neuron. Figure A shows a series of events. Neuron 2 is active (2A) and sends an action potential to neuron 3, which is ready to discharge (3A). In the next time frame, neuron 2 becomes refractory (2B) and cannot be activated for a brief time, and neuron 3 becomes active (3B) and sends an action potential to neuron 4 (4B). If neuron 3 is in the refractory period (3C), then the activity of neuron 2 (2C) will not activate neuron 3. The interactions between two connected oscillators (area B) are based on the principles shown in area A. One oscillator has three nodes and consequently has a higher fundamental frequency than the other five-node oscillator. The sizes of the oscillators (determined by the number of nodes) are different (noncommensurate), which means that their frequencies are not related by some integer. (For example, the frequencies of a two-node and a four-node oscillator are related by the integer 2. In other words, the fundamental frequency of the two-node oscillator is twice the fundamental frequency of the four-node oscillator.) In this example, the frequency and phase of activity in each node of the three-node oscillator are preserved. However, the three-node oscillator periodically injects an extra action potential into the five-node oscillator (clock ticks 5 and 10). The subsequent refractory period in the node of the five-node oscillator receiving input from the three-node oscillator prevents the activity already in the five-node oscillator from continuing (clock ticks 6 and 11). The result is that the overall frequency of the five-node oscillator remains constant but the phase advances.*

influence the magnitude of motor unit recruitment and, thus, the force of muscular contraction. Phases can be reset among oscillators (Figure 14.7). Such phase resetting could have an effect on the strength of muscle contractions, which can be enhanced when different oscillators driving the different motor units cooperate and synchronize their behaviors by phase resetting.

The previous examples show that the dynamic properties and functions of nested oscillators are much greater than the simple one-dimensional, push–pull dynamics of the hierarchical–sequential, excitatory–inhibitory concepts that underlie most current conceptions of physiology and pathophysiology. More research is necessary to prove that the behavior of nested oscillators describes normal and abnormal

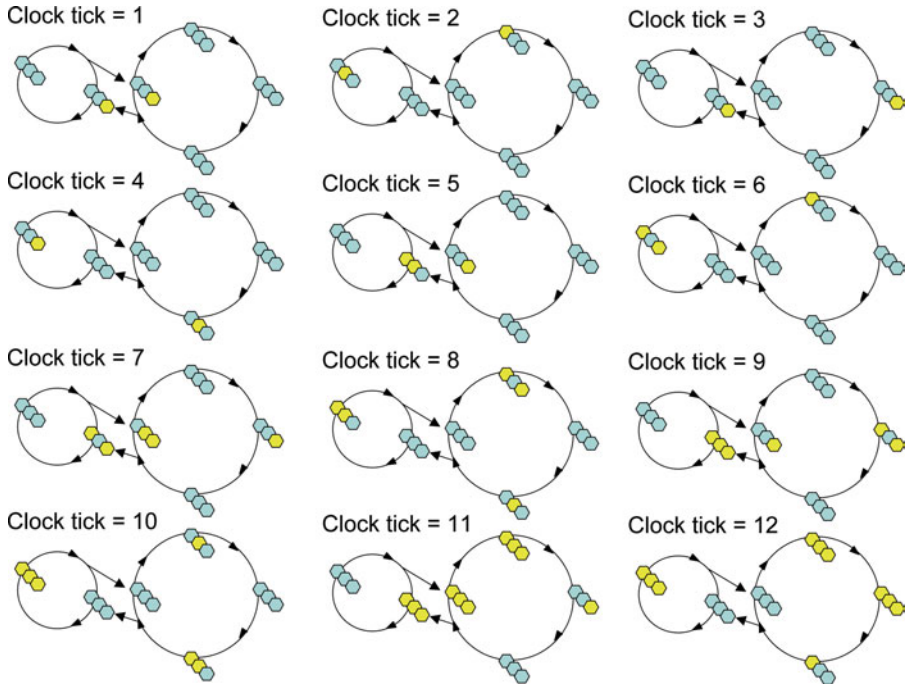

FIGURE 14.6. *An example of the interactions between two oscillators with "commensurate" frequencies. In this case, a two-node oscillator is connected to a four-node oscillator. The neurons that make up each node are shown as hexagons, and each node is represented as a stack of neurons. Blue neurons are inactive, and yellow neurons are active; they generate action potentials that are relayed to the neurons of the next node. The rule is that only one neuron in a node can be activated by an action potential from a neuron in the previous node. Multiple simultaneous inputs activate additional neurons in the receiving node. As the oscillations continue in these commensurate oscillators, the neuronal activities build, as measured by the number of activated neurons within the nodes. This buildup is less likely to occur in the noncommensurate oscillators.*

physiology better than do the push–pull systems, but DBS-related research has already proved the feasibility of characterizing physiology as sets of oscillators.

A remarkable property of networks of large numbers of interconnected oscillators is that they can interact in a great many ways to produce very complex and shifting patterns of activity. Such networks can enter dynamic metastable states, in which the activities within the network are stable, repetitive, or stereotyped, and then they can transition rapidly to very different states. Specific metastable states may be associated with one behavior, and the transitions between metastable states may be associated with changes in the behaviors, such as the orchestration of agonist and antagonist muscles that are necessary for normal movement. Also remarkable is that the same networks (or anatomy) can encode many different behaviors and transitions between behaviors. This notion is very different from that of the one-to-one correspondence between anatomy and function that underlies much of neuroscience (Montgomery, 2004a).

In this chapter, the basal ganglia side loops were discussed as though these side loops are capable of continued sustained oscillations. However, because of the predominance of inhibitory connections in the basal ganglia, the question is raised regarding how such oscillations can be sustained. The answer is that the inhibition of a neuron may be

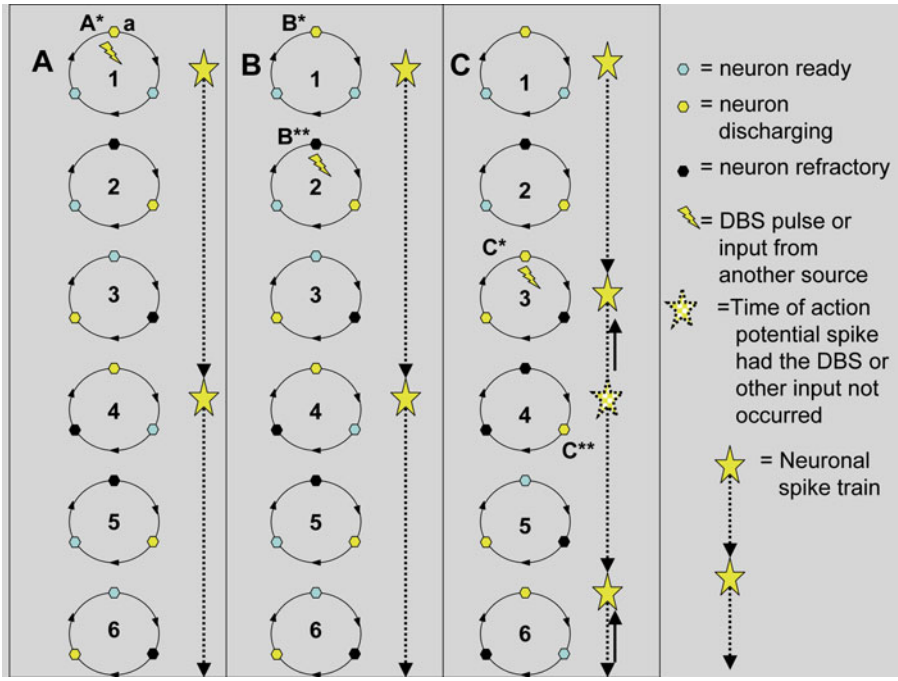

FIGURE 14.7. *The effects of a DBS pulse on a three-node oscillator, given the timing of the pulse relative to the phase of the oscillations. The figure schematically represents the propagation of action potentials through a reentrant three-node oscillator and the effects of the timing of the DBS pulse relative to activity within the three-node oscillator. In column A, the pulse is given to node "a" at the same time there is an action potential in node a (A*). The neuronal spike train of the target node a (represented by the sequence of stars) does not change. In column B, if there are action potentials in the neurons in node a (B*) just before the DBS pulse, neurons in node a will be in their refractory period and not respond to the DBS pulse. The activity will propagate around the oscillator without change. If the DBS pulse is delivered later (C), when the neurons in node a have recovered from the refractory period and are ready, then an action potential will be generated (C*) and propagated through the oscillator (C**). This will result in action potentials occurring in node b and node c earlier (column C) than normal (column A)—hence, a phase advance in the oscillator.*

followed by a postinhibitory rebound excitation (see Commentary 11.1). Consequently, inhibition may be viewed as delayed excitation, thereby allowing reentrant neuronal activities generating oscillations.

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15 Paradoxes in DBS

Despite the remarkable safety and efficacy of DBS (see Commentary 1.1) and progress made in the field of DBS (see Commentary 1.2), little is known about its therapeutic mechanisms of action. Clearly, further research is necessary and highly likely to be enormously beneficial. Concern about the future of DBS and related research necessarily raises the question of how that research will be conducted. The most common approach is to extend what is known, or thought to be known, about the current mechanisms. Much of this research amounts to searching for further examples or higher resolution of measurements. This approach eschews dealing with anomalies or paradoxes and risks the danger in the aphorism, "when all one has is a hammer, the whole world looks like a nail" (Abraham Maslow).

An alternative is to address the anomalies and paradoxes directly. This approach is much more problematic because it is often underdetermined, meaning that there are far fewer hints as to how to proceed, hence the description as anomalous or paradoxical. This underdetermination often generates considerable skepticism by others, particularly those reviewing grant applications. Nonetheless, in my opinion, attacking the paradoxes is most likely to truly advance the field.

How we react to paradoxes in science speaks volumes, and there are plenty of paradoxes to react to in basal ganglia physiology, pathophysiology, and DBS research. In this case, a paradox is an observation that is inconsistent with, or at the least inexplicable by, current theories. Some conservative scientists will continue to promote a theory even in the face of accumulating paradoxes and crumbling support for the theory (Kuhn, 1996). Their reasons for hanging on range from polemical (Kuhn, 1996) to psychological, such as the tendency to prefer a theory that has some explanatory power, even in the face of paradoxes (Johnson-Laird, 2006), as long as the paradoxes do not become too great, whatever that means.

Science has its own "denial" mechanisms for preventing paradoxes from becoming too uncomfortable. These mechanisms include ignoring the paradoxes by not allowing their publication in peer-reviewed journals, by not funding research to explore them, by not inviting scientists who unearth them to present at conferences, and by not addressing them in articles that do get published.

Another mechanism for discounting paradoxes is to attribute them to some unseen error in methods or interpretation. This discounting is easy to do because of the Quine–Duhem theorem, which holds that if the inferences from an observation are in fact wrong, it is impossible to know which of the underlying assumptions is at fault. Consequently, any underlying assumption may be at fault. Thus, the paradoxical finding can be discounted by indicting an assumption, any assumption. And there are always assumptions.

On the other hand, some radical scientists are willing to throw out any theory in the face of any paradox and redirect their research. This mechanism is supported by the concept of *pessimistic induction*, or the belief that because every theory in history has been proven wrong, every theory in the future will also be proven wrong. Solipsism aside, such radicals, although rare, are necessary and need to be supported, if only to prevent conservatism from becoming dogma.

The Paradox of Multiplicity of Targets

DBS targets effective for Parkinson's disease include the globus pallidus internal segment (GPi), globus pallidus external segment, subthalamic nucleus (STN), motor cortex, ventrolateral thalamus, zona incerta, and perhaps more that have yet to be tried. For treating depression, the subgenu cingulum (area 25) as well as the anterior limb of the internal capsule are effective sites. For Tourette's syndrome, DBS of the thalamic nuclei, as well as the GPi, has been reported to be effective (Welter et al., 2008). For each condition, DBS may have as many different mechanisms of action as there are targets, or there may be one (or a few) mechanism(s) in which multiple structures are involved; in other words, some targets may have a systems effect rather than a target effect. The systems effect is the most parsimonious. However, the large majority of theories about the mechanisms of action have focused on the DBS target rather than on a systems effect (Lozano and Eltahawy, 2004; McIntyre and Thakor, 2002; Montgomery and Gale, 2008).

The Paradox of Variability in DBS Frequency Effects

Until recently, the prevailing notion of DBS effects was that high-frequency DBS helped and that low-frequency DBS worsened. There is now considerable evidence to the contrary (see Commentary 5.1). More paradoxical is the fact that, at least in nonhuman primates, the immediate neuronal response to the STN DBS pulse is qualitatively the same, regardless of the frequency of DBS (Montgomery and Gale, 2008). However, there does appear to be a qualitative difference. At least in nonhuman primates, STN DBS at 130 pps produces a greater response than does DBS at 100 or 50 pps (Montgomery and Gale, 2008). An STN DBS pulse delivered approximately 7 ms before a subsequent DBS pulse (in the case of 130-pps DBS) produces a different response to the subsequent pulse than that obtained when the previous pulse is given 10 ms (for 100-pps DBS) or 20 ms (for 50-pps DBS) before a subsequent DBS pulse.

The Paradox of Variability in Latency Periods of DBS Effects

Tremor visibly responds to the onset of therapeutically effective DBS within seconds. Bradykinesia, in the case of Parkinson's disease, and dyskinesia may take seconds to respond. Gait and postural abnormalities may take many minutes to respond (see Chapter 13). Various theories of the mechanisms of action of DBS do contain elements that may explain differences in latencies. For example, depolarization blockage, in which a period of subthreshold depolarization that is insufficient to generate an action potential but inactivates sodium ion conductance channels, would

delay an action potential. Similarly, if DBS depletes the presynaptic terminals of neurotransmitters (Lozano and Eltahawy, 2004), results in an accumulation of inhibitory neurotransmitters, or is applied during the accumulation of adenosine (Bekar et al., 2008), latencies could occur. However, although each of these notions may explain the presence of a latency, they do not explain the variability among latencies. These notions would have to be reworked to explain the fact that the thresholds needed to improve tremor, bradykinesia, and gait are different (see Chapter 13).

The Paradox of the U-Shaped Response

The U-shaped response describes a progressive improvement in the symptoms of Parkinson's disease with increasing strength of DBS (increasing voltage) that is followed by a worsening with further increases in DBS strength (see Commentary 6.1). Initially, the worsening was thought to represent the spread of stimulation to the internal capsule from either the STN or the GPi. However, studies have found that this explanation is unlikely for at least some instances of the U-shaped response (Montgomery and Sillay, 2008).

In one-dimensional, push–pull theories of the mechanisms of action of DBS, such as DBS causing a loss of neuronal activation through depolarization blockage, neurotransmitter release, or adenosine accumulation, loss of activation should vary with the strength of DBS. For example, these theories suggest that increased DBS strength would only further reduce neuronal activation and should therefore improve, not worsen, its clinical effects. In contrast, the Systems Oscillators theory does provide a possible explanation for this response (see Commentary 6.1).

The Paradox of Dissociating the Neurometabolic from the Electrophysiological Effects of DBS

Numerous neurometabolic studies of the response to DBS, such as positron emission tomography, have found reductions in markers of cerebral blood flow in the motor cortex and supplementary motor area. For patients with Parkinson's disease at rest and without stimulation, regional cerebral blood flow is consistency higher than that in the ipsilateral primary motor cortex. Therapeutic (high-frequency) STN DBS decreases regional cerebral blood flow in the ipsilateral primary motor cortex (Ceballos-Baumann et al., 1999; Payoux et al., 2004). Some studies have found that regional cerebral blood flow is also decreased in the lateral premotor cortex, the right cerebellum, and the midline premotor areas (Payoux et al., 2004). Other studies of changes in blood flow in response to motor activation have found enhanced movement-related changes in blood flow in the rostral premotor areas and dorsal prefrontal cortex (Ceballos-Baumann et al., 1999). The selective activation of the anterior cingulate cortex and the left primary sensorimotor cortex during hand movement under STN DBS has been attributed to decreased regional cerebral blood flow at rest rather than increased activation induced by high-frequency stimulation of the DBS (Payoux et al., 2004). Neuroimaging studies reveal a reduction in regional cerebral blood flow that parallels the therapeutically effective STN DBS frequencies (Haslinger et al., 2003). However, cortical evoked potential studies

and electromyographic studies show a direct effect on cortical activations (Ashby et al., 1999; Baker et al., 2002). Furthermore, direct recording from the motor cortex in nonhuman primates receiving STN DBS has documented direct antidromic activation (Montgomery and Gale, 2008). Recordings of ventrolateral thalamic neurons in a human receiving GPi DBS show antidromic activation and postinhibitory rebound activation that could then directly drive the motor cortex (Montgomery, 2006).

One potential explanation for the discrepancy between the neurometabolic and electrophysiologic observations derives from studies showing how the mechanisms of neuronal activation determine the neurometabolic response. The coupling depends on whether one considers local field potentials, representing input functions that reflect afferent inputs to dendritic synapses, or whether one considers extracellular action potentials, which represent output functions (Logothetis, 2007; Viswanathan and Freeman, 2007). Particularly striking is the observation that orthodromic activity increased metabolism, whereas antidromic activity did not (Logothetis, 2007). Thus, as posited by the Systems Oscillators theory, a substantial effect of DBS may be related to antidromic activation of various structures, particularly the motor cortex (see Commentary 3.2), resulting in smaller increases in metabolism that could be seen as reduced blood flow.

The Paradox of the "Dumb" Constant-Frequency DBS That Yet Restores Information

From an information-theoretic perspective, the restoration of motor function, or any other behavior, can be viewed as an improvement in information processing. The lower motor neurons must receive the correct information and translate it into the orchestrated activations of various synergistic muscles. Indeed, disease can be thought of as misinformation rather than as the traditional loss or excess of function. Thus, incorrect information transmitted to the lower motor neurons is characterized by the failure to properly orchestrate muscle activations and the consequent motor symptoms of Parkinson's disease.

The traditional notions of loss or excess of function alone result in false dichotomies, such as bradykinesia and hyperkinesias being reciprocal and, consequently, that the mechanistic physiological accounts are likewise reciprocal. Several authors have argued that overactivity of the GPi results in bradykinesia and that underactivity of the GPi results in hyperkinesia. However, the effectiveness of pallidotomy, as well as that of GPi DBS, on both bradykinesia and hyperkinesia is strong evidence against the theories that utilize this dichotomy (Montgomery, 2007a).

Again from an information-theoretic perspective, continuous and regular DBS imparts no information. Consider the analogy of Morse code, in which information is encoded in a sequence of dots and dashes. Regular DBS would be analogous to a continuous flow of only dots or only dashes and consequently could not encode any information. How can a signal injected into the brain that contains no information (no variation) improve the information being conveyed to the lower motor neurons?

Several hypotheses for this process have been proposed. First, DBS may convert the output of the stimulated target from misinformation to no information, which is

better tolerated by the brain (see Figure 14.4 and its discussion in the text) (Grill et al., 2004; Montgomery and Baker, 2000).. Second, regular or constant frequency DBS at specific frequencies resonates with and amplifies the signal above the background noise, thereby increasing the information content of the signals in the stimulated network (see Figure 14.4 and its discussion in the text; see also Commentary 5.1).

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Appendix 1

Index to DBS Side Effects, by Side Effect and Site of Stimulation

By Side Effect

By DBS Site

Appendix 2

Aids to Programming: Paper Documentation

The following pages are sample forms for documenting clinical responses to DBS programming. Electronic versions of the forms can be downloaded from www.XXX.XXX.

There are two aspects to the forms—diagnosis and DBS target site. As indications and targets expand, additional rating forms can be developed. For example, evidence indicates that DBS of the subthalamic nucleus (STN) and the globus pallidus interna (GPi) can treat dystonia.

The forms contain columns for the electrode configuration, DBS stimulation parameters, common side effects specific to the DBS target, and clinical ratings specific to the disease. A column in the side effect section is entitled "Other" (Figure A2.1). Unlisted side effects can be numbered in this column at the appropriate row and be described elsewhere in a numbered note.

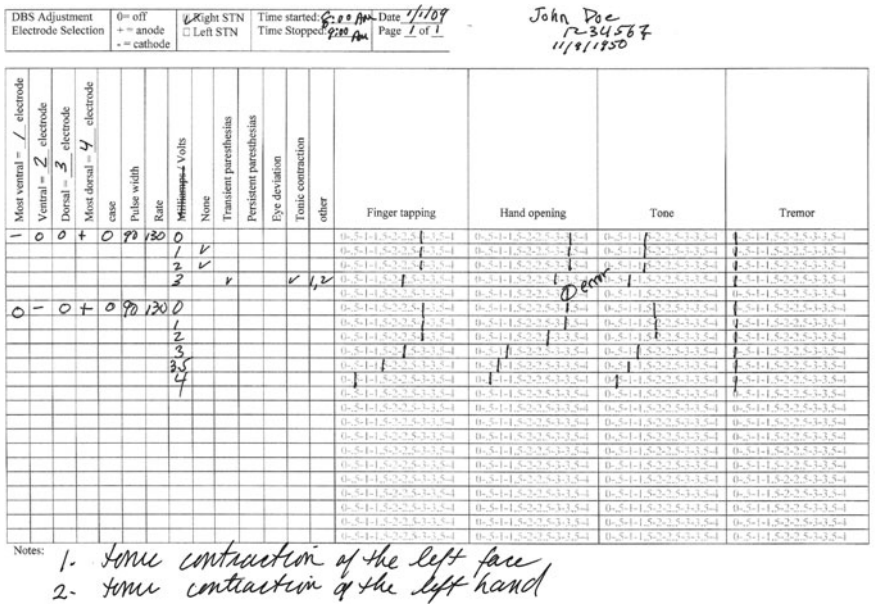

FIGURE A2.1. *An example of documenting STN DBS in a patient with Parkinson's disease. The first five columns indicated the active contact configuration. Note that there are five sets of possible configurations depending on the naming convention (see Figure A3.1). The naming configurations not relevant to this particular patient's IPG have been entered.. The next three columns indicate the stimulation parameters. The next six columns indicate the common side effects to STN DBS. There is one column labeled "Other." This allows you to document any other side effects. Typically, a footnote number is entered into the column for as many other side effects, and the other side effects are described in the "Notes" section at the bottom. The next four columns identify four main symptoms and signs responding to STN DBS. The grading system for each symptom and sign is listed below. A vertical hash mark is made to grade the clinical response. As can be seen, the initial electrode configuration produced limiting side effects. Once the configuration was changed, there was a progressive improvement in the patient's symptoms and signs. However, the optimal voltage was greater than the battery voltage of the patient's IPG and, consequently, another electrode parameter should be attempted, such as an increase in the DBS frequency.*

Parkinson's Disease

The majority of Parkinson's disease patients undergo either STN or GPi DBS. Forms specifically for documenting stimulation to the STN and GPi are given later. Clinical assessments for patients with Parkinson's disease are based on subtests of the motor examination of the Unified Parkinson's Disease Rating Scale, part III (Fahn et al., 1987). Guides to the quantification are as follows:

Finger tapping (rapidly tapping index finger to the thumb)

0 = Normal.
1 = Mild slowing or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

Hand opening (and closing)

0 = Normal.
1 = Mild slowing or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

Tone (resistance to passive flexion and extension of a joint, typically at the elbow)

0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

Tremor at rest

0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

Other symptoms that are often tested include postural stability, postural reflexes, and gait:

0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

DBS Adjustment STN PD

DBS Adjustment Electrode Selection	0= off + = anode - = cathode	☐ Right STN ☐ Left STN	Time started: ______ Time Stopped: ______	Date_______ Page __ of __	Patient name:______________________________ Medical Record no. ___________________________. Date of Birth: ______________________________

Most ventral = ____ electrode	Ventral = ____ electrode	Dorsal = ____ electrode	Most dorsal = ____ electrode	case	Pulse width	Rate	Milliamps / Volts	None	Transient paresthesias	Persistent paresthesias	Eye deviation	Tonic contraction	other	Finger tapping	Hand opening	Tone	Tremor
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

DBS Adjustment GPi PD

DBS Adjustment Electrode Selection	0= off + = anode - = cathode	□ Right GPi □ Left GPi	Time started: ______ Time Stopped: ______	Date_______ Page __ of __	Patient name:______________________________ Medical Record no. ___________________________. Date of Birth: ______________________________

Most ventral = ___ electrode	Ventral = ___ electrode	Dorsal = ___ electrode	Most dorsal = ___ electrode	case	Pulse width	Rate	Milliamps / Volts	None	phosphenes	Tonic contraction	Speech problems	Diplopia or eye deviation	other	Finger tapping	Hand opening	Tone	Tremor
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

Cerebellar Outflow Tremor or Essential Tremor

The following rating scales for evaluating patients undergoing thalamic DBS to treat tremor are based on the Clinical Rating Scale for Tremor (Fahn et al., 1993):

Resting tremor: Assessed in the upper extremities with the hands resting on the lap.

Postural tremor: Assessed with the upper extremities held extended in front of the patient.

Action tremor: Assessed with the upper extremities held extended in front of the patient and then the index finger is brought to the patient's nose and to the examiner's finger held in front of the patient in an alternating manner.

Cup task: The patient reaches to a cup held in front of him or her, grasps the cup, and brings the cup to his or her lips as if to drink from the cup.

The degree of tremor is rated as follows:

0 = No tremor.
1 = Barely perceptible or intermittent tremor.
2 = Tremor amplitude less than 2 cm.
3 = Tremor amplitude of 2–4 cm.
4 = Tremor greater than 4 cm or the patient was unable to perform the task.

The Food and Drug Administration (FDA) has *not* approved DBS for treating tremor secondary to causes other than Parkinson's disease and essential tremor. However, considerable evidence suggests that thalamic DBS is safe and effective (Montgomery, 2008a), and it is considered standard and accepted "off-label" treatment when using IPGs FDA-approved for other conditions.

Dystonia

The majority of patients with dystonia undergo GPi DBS, although the use of STN DBS is increasing. Below are forms specific to documenting such treatment. Clinical assessments for patients with dystonia are based on subtests of the motor examination of the Unified Dystonia Rating Scale (Dystonia Study Group, 1997). The forms are designed to document dystonia that affects up to four different muscle groups. These forms are specifically modified by the user for each patient according to the type of dystonia being treated. Guides to quantifying the dystonia are given here. Patients can be assessed at rest, as in cervical dystonia, or while attempting a specific task, such as reaching for a cup. To assess the degree of abnormality, visualize the normal or neutral position and the normal range of motion of the body part and then estimate the degree of departure from normal or neutral position as a percentage of the normal range of motion about that body part.

0 = None.
1 = Mild: Movements of affected muscle group $<25\%$ of possible normal range.
2 = Moderate: Movements of affected muscle group 25% but $<50\%$ of possible normal range.

DBS Adjustment Vim tremor

DBS Adjustment Electrode Selection	0= off + = anode - = cathode	☐ Right Vim ☐ Left Vim	Time started: ______ Time Stopped: ______	Date________ Page __ of __

Patient name:____
Medical Record no. ____________________________________.
Date of Birth: ____

Most ventral = ___ electrode	Ventral = ___ electrode	Dorsal = ___ electrode	Most dorsal = ___ electrode	case	Pulse width	Rate	Milliamps / Volts	None	Transient paresthesias	Persistent paresthesias	Speech problems	Tonic contraction	other	Resting tremor	Postural tremor	Action tremor	Cup task
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

3 = Severe: Movements of affected muscle group 50% but <75% of possible normal range.
4 = Extreme: Movements of affected muscle group >75% of possible normal range.

There are special cases that are graded differently as follows:

Larynx
0 = None.
1 = Mild: Barely detectable hoarseness or choked voice or occasional voice breaks.
2 = Moderate: Obvious hoarseness or choked voice or frequent voice breaks.
3 = Severe: Marked hoarseness or choked voice or continuous voice breaks.
4 = Extreme: Unable to vocalize.

Eyes and upper face
0 = None.
1 = Mild: Increased blinking or slight forehead wrinkling (<25% maximal intensity).
2 = Moderate: Eye closure without squeezing or pronounced forehead wrinkling (>25% but <50% maximal intensity).
3 = Severe: Eye closure with squeezing, able to open eyes within 10 seconds or marked forehead wrinkling (>50% but <75% maximal intensity).
4 = Extreme: Eye closure with squeezing, unable to open eyes within 10 seconds or intense forehead wrinkling (>75% maximal intensity).

Lower face
0 = None.
1 = Mild: Grimacing of lower face with minimal distortion of mouth (<25% maximal).
2 = Moderate: Grimacing of lower face with moderate distortion of mouth (>25% but <50% maximal).
3 = Severe: Marked grimacing with severe distortion of mouth (>50% but <75% maximal).
4 = Extreme: Intense grimacing with extreme distortion of mouth (>75% maximal)

Dyskinesia

Most patients with dyskinesia undergo GPi DBS. The forms are specific to GPi and allow recording treatment for dyskinesia that affects up to four different muscle groups. Guides to the quantification of the dyskinesia are given later. Patients can be assessed while performing a specific task, depending on the muscle group being assessed, such as reaching for a cup with the hand and arm.

0 = No dyskinesia.
1 = Minimal severity, no interference with volitional task.
2 = Dyskinesia may impair performance, but the task can be completed without significant difficulty.

DBS Adjustment GPi dystonia

DBS Adjustment Electrode Selection	0= off + = anode - = cathode	□ Right GPi □ Left GPi	Time started: ______ Time Stopped: ______	Date_______ Page __ of __	Patient name: ______________________________ Medical Record no. ___________________________. Date of Birth: ______________________________

Most ventral = ____electrode	Ventral = ____ electrode	Dorsal = ____ electrode	Most dorsal = ____ electrode	case	Pulse width	Rate	Milliamps / Volts	None	phosphenes	Tonic contraction	Speech problems	Diplopia or eye deviation	other	Dystonia 1 Describe __________ ________________ ________________	Dystonia 2 Describe __________ ________________ ________________	Dystonia 3 Describe __________ ________________ ________________	Dystonia 4 Describe __________ ________________ ________________
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

DBS Adjustment STN dystonia

DBS Adjustment Electrode Selection	0= off + = anode - = cathode	□ Right STN □ Left STN	Time started: ______ Time Stopped: ______	Date_______ Page __ of __	Patient name:________________________ Medical Record no. ___________________. Date of Birth: ______________________

Most ventral = ___ electrode	Ventral = ___ electrode	Dorsal = ___ electrode	Most dorsal = ___ electrode	case	Pulse width	Rate	Milliamps / Volts	None	Transient paresthesias	Persistent paresthesias	Eye deviation	Tonic contraction	other	Dystonia 1 Describe __________ ________________ ________________ ________________	Dystonia 2 Describe __________ ________________ ________________ ________________	Dystonia 3 Describe __________ ________________ ________________ ________________	Dystonia 4 Describe __________ ________________ ________________ ________________
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

DBS Adjustment GPi dyskinesia

DBS Adjustment Electrode Selection	0= off + = anode - = cathode	☐ Right GPi ☐ Left GPi	Time started: ______ Time Stopped: ______	Date_______ Page __ of __	Patient name:___________________________ Medical Record no. ______________________. Date of Birth: ___________________________

Most ventral = ___ electrode	Ventral = ___ electrode	Dorsal = ___ electrode	Most dorsal = ___ electrode	case	Pulse width	Rate	Milliamps / Volts	None	phosphenes	Tonic contraction	Speech problems	Diplopia or eye deviation	other	Dyskinesia 1 Describe __________ _________________ _________________	Dyskinesia 2 Describe __________ _________________ _________________	Dyskinesia 3 Describe __________ _________________ _________________	Dyskinesia 4 Describe __________ _________________ _________________
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

DBS Adjustment GPi Tics

DBS Adjustment Electrode Selection	0= off + = anode - = cathode	□ Right GPi □ Left GPi	Time started: ______ Time Stopped: ______	Date_______ Page __ of __	Patient name:___________________________ Medical Record no. _______________________. Date of Birth: ___________________________

Most ventral = ___ electrode	Ventral = ___ electrode	Dorsal = ___ electrode	Most dorsal = ___ electrode	case	Pulse width	Rate	Milliamps / Volts	None	phosphenes	Tonic contraction	Speech problems	Diplopia or eye deviation	other	Tic 1 Describe __________ ________________ ________________	Tic 2 Describe __________ ________________ ________________	Tic 3 Describe __________ ________________ ________________	Tic 4 Describe __________ ________________ ________________
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

DBS Adjustment STN Tics

DBS Adjustment Electrode Selection	0= off + = anode - = cathode	☐ Right STN ☐ Left STN	Time started: ______ Time Stopped: ______	Date_______ Page __ of __	Patient name:________________________ Medical Record no. ____________________. Date of Birth: ______________________

Most ventral = ___ electrode	Ventral = ___ electrode	Dorsal = ___ electrode	Most dorsal = ___ electrode	case	Pulse width	Rate	Milliamps / Volts	None	Transient paresthesias	Persistent paresthesias	Eye deviation	Tonic contraction	other	Tic 1 Describe __________ __________________ __________________ __________________	Tic 2 Describe __________ __________________ __________________ __________________	Tic 3 Describe __________ __________________ __________________ __________________	Tic 4 Describe __________ __________________ __________________ __________________
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4
														0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4	0-.5-1-1.5-2-2.5-3-3.5-4

Notes:

3 = Dyskinesia significantly impairs performance of the task, which can be completed only with great difficulty.
4 = Dyskinesia prevents the patient from performing the task.

The FDA has *not* approved DBS for the treatment of dyskinesia. However, considerable evidence suggests that GPi DBS is safe and effective (Montgomery, 2004b), and it is considered to be a standard and accepted off-label use when using FDA devices approved for other conditions.

Tourette's Syndrome

Most patients with Tourette's syndrome undergo GPi DBS. The following forms are specific to GPi and allow recording treatment for Tourette's syndrome that affects up to four different tics. The user can modify the columns depending on the patient's specific manifestations. Guides to the quantification of the tics are as follows:

0 = No tics.
1 = <3 tics per minute of observation.
2 = 3–6 tics per minute of observation.
3 = 7–10 tics per minute of observation.
4 = >10 tics per minute of observation.

The FDA has *not* approved DBS for treating Tourette's syndrome. However, considerable evidence suggests that GPi DBS is safe and effective for Tourette's syndrome, as with other hyperkinetic disorders (Montgomery, 2004b), and it is considered standard and accepted off-label use when using FDA devices approved for other conditions. There is some experience suggesting that STN DBS is effective as well and would be considered "off-label" use of a FDA-approved device. Appropriate rating forms are provided.

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Appendix 3

Aid to Programming: Algorithm and Checklist for Electrode Configurations

Patient name: _____ Medical record No. _____

Date of birth: Month _____ Day _____ Year _____

Diagnosis: _____ DBS target: _____

DBS side: _____

The designations for the contacts used here assume that the DBS lead contains four potential cathodes arranged linearly along the axis of the lead. The contacts are designated as most ventral, ventral, dorsal, and most dorsal (Figure A3.1). Electrode configurations are described as monopolar (DBS lead contacts as cathodes and the IPG as anode), wide bipolar (both anode and cathodes on the DBS lead and there are two contacts between the anode and the cathodes), close bipolar (both anode and cathodes on the DBS lead and there is one contact between the anode

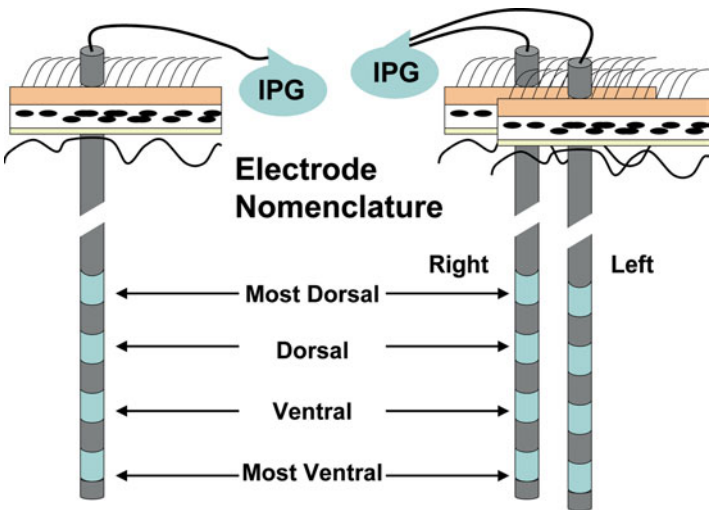

FIGURE A3.1. *Nomenclature of a DBS lead with four contacts. Manufacturers often number the contacts, but the conventions vary among manufactures. Given the already large number of variations in numbering, this monograph will refer to contacts by their relative location and not number. However, on the programming documentation forms, there are provisions to allow the programmer to assign the appropriate contact numbers. These discussions of electrode configurations assume that the DBS lead consists of a linear array along the long axis of the DBS lead, as depicted in the figures. The general principles described here also apply to other types of DBS leads, although the specific algorithms may differ. You should consult the manufacturer of the DBS leads you intend to use.*

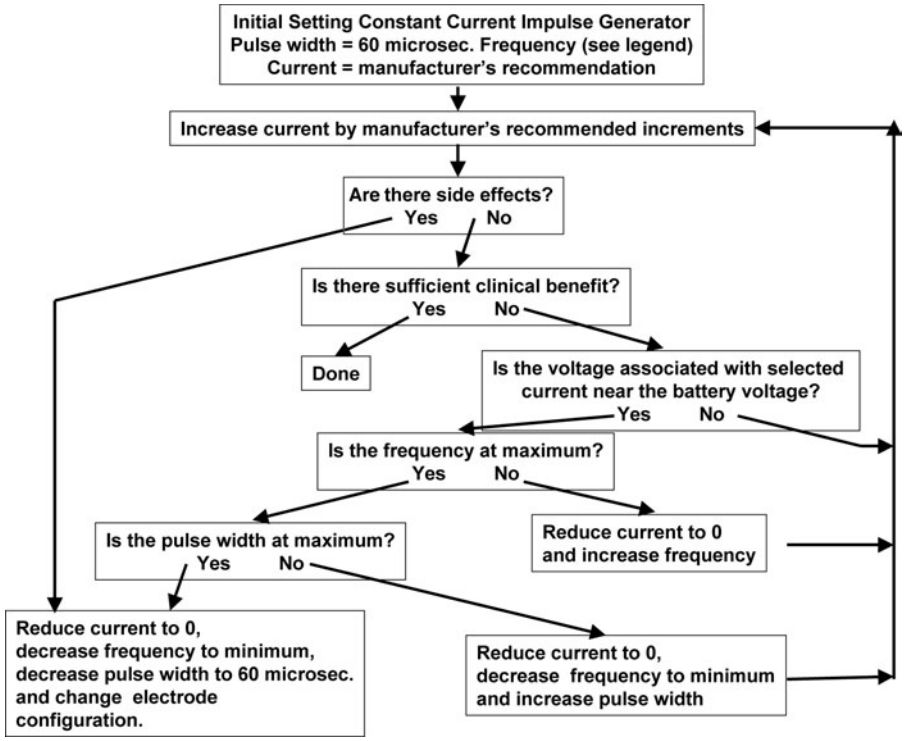

FIGURE A3.2. *Algorithm for adjusting stimulation parameters for any specific electrode configuration for constant-current IPGs. The initial DBS frequency will vary depending on DBS target and disease. For general use in Parkinson's disease, essential tremor, dystonia, Tourette's syndrome, hyperkinetic disorders in general, and cerebellar outflow tremor, the initial frequency would be 130 pps. For patients with Parkinson's disease who experience worsening of gait or speech with high-frequency DBS, an initial DBS frequency would be 60 pps. For patients with dystonia who do not improve with the typical high frequencies, 60 pps GPi DBS may be helpful. In the future, pedunculopontine (PPN) DBS may be employed, in which initial DBS frequencies of 40 pps are used. Note, the algorithm recommendations regarding stimulation currents are based on optimizing battery life (see Optimizing Battery Life, Chapter 2. Principles of DBS Electronics. However, with the plethora of IPGs, the battery efficiencies relative to stimulation current make recommendations problematic. Until such issues are clarified, the algorithms are based on the understanding that increasing stimulation current above the level whether the necessary stimulation voltage necessary to achieve the stimulation current exceeds the IPG battery voltages is less efficient. However, it higher currents are necessary for patient efficacy, these should be use.*

and the cathodes), and narrow bipolar (both anode and cathodes on the DBS lead and there are no contacts between the anode and the cathodes).

1.0 Start
Single cathode (−) monopolar
Most ventral contact cathode (−); case anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 1.1 ___ yes ___ no
No efficacy go to 1.1 ___ yes ___ no
___ Done if checked

Comments: _____

_____

_____

_____

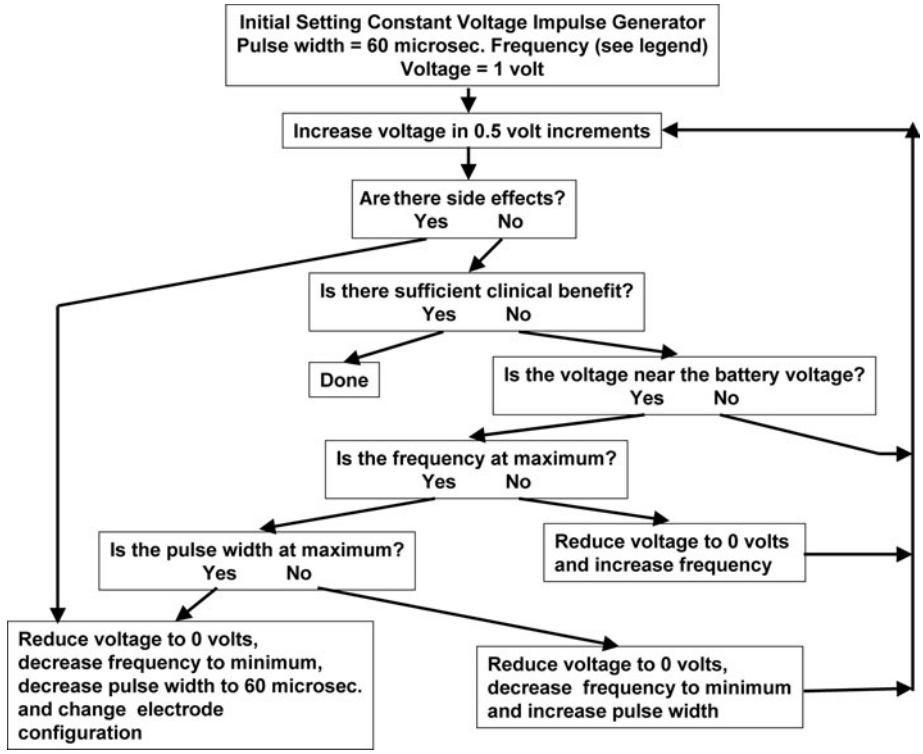

FIGURE A3.3. *Algorithm for adjusting stimulation parameters for any specific electrode configuration for constant-voltage IPGs. The initial DBS frequency will vary depending on DBS target and disease. For general use in Parkinson's disease, essential tremor, dystonia, Tourette's syndrome, hyperkinetic disorders in general, and cerebellar outflow tremor, the initial frequency would be 130 pps. For patients with Parkinson's disease who experience worsening of gait or speech with high-frequency DBS, an initial DBS frequency would be 60 pps. For patients with dystonia who do not improve with the typical high frequencies, 60 pps GPi DBS may be helpful. In the future, pedunculopontine (PPN) DBS may be employed, in which initial DBS frequencies of 40 pps are used. Note, the algorithm recommendations regarding stimulation voltage are based on optimizing battery life (see Optimizing Battery Life, Chapter 2. Principles of DBS Electronics. However, with the plethora of IPGs, the battery efficiencies relative to stimulation current/voltage make recommendations problematic. Until such issues are clarified, the algorithms are based on the understanding that increasing stimulation voltage above the IPG battery voltages is less efficient. However, it higher voltages are necessary for patient efficacy, these should be use.*

1.1 Single cathode (−) monopolar
Ventral contact cathode (−); case anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 1.2 __ yes __ no
No efficacy go to 1.2 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

1.2 Single cathode (−) monopolar
Dorsal contact cathode (−); case anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 1.3 __ yes __ no
No efficacy go to 1.3 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

1.3 Single cathode (−) monopolar
Most dorsal contact cathode (−); case anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 2.0 __ yes __ no
No efficacy go to 2.0 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

2.0 Wide bipolar polar
Most ventral contact cathode (−); most dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 2.1 __ yes __ no
No efficacy go to 2.1 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

2.1 Wide bipolar polar
Most ventral contact anode (+); most dorsal contact cathode (−)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 5.0 __ yes __ no
No efficacy go to 3.0 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

3.0 Multiple cathodes (−) monopolar
Most ventral and ventral contacts cathode (−); case anode (+)
Check therapeutic impedances
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 3.1 __ yes __ no
No efficacy go to 3.2 __ yes __ no
__ Done if checked

Comments: _____

_____

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_____

3.1 Multiple cathodes (−) monopolar
Ventral and dorsal contacts cathode (−); case anode (+)
Check therapeutic impedances
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 3.3 __ yes __ no
No efficacy go to 3.3 __ yes __ no
__ Done if checked

Comments: _____

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_____

3.2 Multiple cathodes (−) monopolar
Dorsal and most dorsal contacts cathode (−); case anode (+)
Check therapeutic impedances
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 5.0 __ yes __ no
No efficacy go to 4.0 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

4.0 Wide multiple cathode (−) bipolar
Most ventral and ventral contacts cathode (−); most dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 4.1 __ yes __ no
No efficacy go to 4.2 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

4.1 Wide multiple cathode (−) bipolar
Most dorsal and dorsal contact cathodes (−); most ventral contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 4.3 __ yes __ no
No efficacy: Check system for hardware failure, check DBS lead location for poor location __ yes __ no
__ Done if checked

Comments: _____

_____

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5.0 Close single cathode (−) bipolar
Most ventral contact cathode (−); dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 5.1 __ yes __ no
No efficacy go to 5.1 __ yes __ no
__ Done if checked

Comments: _____

_____

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_____

5.1 Close single cathode (−) bipolar
Ventral contact cathode (−); most dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 5.2 __ yes __ no
No efficacy go to 5.2 __ yes __ no
__ Done if checked

Comments: _____

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_____

5.2 Close single cathode (−) bipolar
Most dorsal contact cathode (−); ventral contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 5.3 __ yes __ no
No efficacy go to 5.3 __ yes __ no
__ Done if checked

Comments: _____

_____

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_____

5.3 Close single cathode (−) bipolar
Dorsal contact cathode (−); most ventral contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 7.0 __ yes __ no
No efficacy go to 6.0 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

6.0 Close multiple cathodes (−) bipolar
Most ventral and ventral contacts cathode (−); dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 6.1 __ yes __ no
No efficacy go to 6.1 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

6.1 Close multiple cathodes (−) bipolar
Ventral and dorsal contacts cathode (−); most dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 6.2 __ yes __ no
No efficacy go to 6.2 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

6.2 Close multiple cathodes (−) bipolar
Most dorsal and dorsal contact cathodes (−); ventral contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 6.3 __ yes __ no
No efficacy go to 6.3 __ yes __ no
__ Done if checked

Comments: _____

_____

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_____

6.3 Close multiple cathodes (−) bipolar
Dorsal and ventral contacts cathodes (−); most ventral contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 7.0 __ yes __ no
No efficacy: Check system for hardware failure, check DBS lead location for poor locations __ yes __ no
__ Done if checked

Comments: _____

_____

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_____

7.0 Narrow single cathode (−) bipolar
Most ventral contact cathode (−); ventral contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 7.1 __ yes __ no
No efficacy go to 7.1 __ yes __ no
__ Done if checked

Comments: _____

_____

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7.1 Narrow single cathode (−) bipolar
Ventral contact cathode (−); dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 7.2 __ yes __ no
No efficacy go to 7.2 __ yes __ no
__ Done if checked

Comments: _____

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_____

7.2 Narrow single cathode (−) bipolar
Dorsal contact cathode (−); most dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 7.3 __ yes __ no
No efficacy go to 7.3 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

7.3 Narrow single cathode (−) bipolar
Ventral contact cathode (−); most ventral contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 7.4 __ yes __ no
No efficacy go to 7.4 __ yes __ no
__ Done if checked

Comments: _____

_____

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7.4 Narrow single cathode (−) bipolar
Dorsal contact cathode (−); ventral contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 7.5 __ yes __ no
No efficacy go to 7.5 __ yes __ no
__ Done if checked

Comments: _____

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7.5 Narrow single cathode (−) bipolar
Most dorsal contact cathode (−); dorsal contact anode (+)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 8.0 __ yes __ no
No efficacy: Check system for hardware failure, check DBS lead location for poor location __ yes __ no
__ Done if checked

Comments: _____

_____

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_____

8.0 Narrow multiple anodes (+) bipolar
Dorsal and most ventral contacts anodes (+); ventral contact cathode (−)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect go to 8.1 __ yes __ no
No efficacy go to 8.1 __ yes __ no
__ Done if checked

Comments: _____

_____

_____

_____

8.1 Narrow multiple anodes (+) bipolar
Most dorsal and ventral contacts anodes (+); dorsal contact cathode (−)
Increase parameters as shown in Figures A3.2 and A3.3
Side effect: At this point, interleaved configurations and parameters should be tried. The stimulation current/voltage can be apportioned based on the

side effect profile and efficacy. For example, if stimulation of the most ventral contact provided greater efficacy but with significant side effects, whereas the ventral contact produced less efficacy but no side effects, the first step would be to apply the maximum stimulation current/voltage tolerated on the most ventral contact and then the maximum stimulation current/voltage tolerated on the ventral contact and determine whether this resulted in sufficient efficacy without significant side effects. __ yes __ no

If this fails, check system for hardware failure, confirm correct DBS lead location __ yes __ no

Check system for hardware failure, check DBS lead location for poor location __ yes __ no

No efficacy: Check system for hardware failure, check DBS lead location for poor location __ yes __ no

__ Done if checked

Comments: _____

_____

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_____

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Glossary

action potential A specific change in the electrical potential of the neuronal membrane that is propagated down the axon of one neuron to affect subsequent neurons. The action potential is a basic unit of information, such as the 0's and 1's of a computer or the dots and dashes of Morse code. Information is encoded in the sequence of action potentials. This information from one neuron is translated into postsynaptic excitatory or inhibitory synaptic potentials in the next set of neurons. These neurons then integrate the post-synaptic potentials (information processing) and translate the results to another set of action potentials, which are relayed further through the network of neurons.

amperage (current) A measure of electrical current; the number of electrons moving past a point in a given period of time.

anodal Adjective referring to the electrically positive component of the stimulation pulse or current. Typically anodal refers to the return of electrical changes to the anode or positive contact that were released at the cathode or negative contact

anode The electrically positive contact.

antidromic Nerve impulses conducted in a direction opposite to the usual one. Typically, these action potentials are conducted up the axon towards the neuronal cell body or soma in contrast to the normal conduction away from the cell body.

cathodal Adjective referring to the electrically negative component of the stimulation pulse or current. Typically, this refers to the release of negative charges from the cathode or negative contact of an electrode.

cathode The electrically negative contact.

charge density The amount of electrical charge delivered during the cathodal (negative) or absorbed during the anodal (positive) phase of the stimulation pulse divided by the surface area of the electrical contact.

coulombs The total amount of electrical charge delivered over time.

current (amperage) The number of electrons or negative charges flowing per second.

electrode A structure, typically metal, for delivering electrical current. An electrode should not be confused for the DBS lead, which is an arrangement of electrodes of which some or all may be active in delivering electrical current.

electrode configuration The specific combination of active contacts (anodes and cathodes) in the DBS lead and IPG case. This does not include the stimulation parameters such as current/voltage, pulse width, or stimulation frequency (rate).

electrode impedance The resistance to the flow of electrical charge with each monopolar and bipolar configuration. The voltage, pulse width, and frequencies used to determine electrode impedances are generally not the same as those used in therapeutic DBS.

electrolysis A process in which water molecules are broken down into hydrogen and oxygen gas bubbles; a mechanism by which DBS can damage brain tissue.

Hertz A measure of frequency; here, of electrical waveforms, typically in pulses or cycles per second.

impedance The resistance to the flow of electrical charge typically associated with a varying voltage or current source—for example, alternating current (AC) rather than direct current (DC).

lead An arrangement of electrodes of which some or all may be active in delivering electrical current. An electrode should not be confused for the DBS lead.

orthodromic Nerve impulses conducted in the usual direction down the axon away from the neuronal cell body or soma.

phase In the context of a DBS pulse, phase refers to the part of the DBS pulse associated with one polarity of electrical current. The negative (cathodal) phase is associated with negative electrical charges flowing from the electrical contact. A positive (anodal) phase is associated with negative electrical charges flowing into the contact. In the context of describing a periodic function, phase refers to the location in a wave relative to some initial reference point and can be measured in time (seconds) or in degrees.

phosphenes Bright flashing lights in the visual fields that are not caused by external light sources.

power spectra A manner of representing the energy or power of different frequencies in any signal. For example, any complex varying signal can be decomposed into a series of sine waves, each with a specific frequency. The amount of each component frequency in the original complex signal is represented in the power spectra.

pulse width The duration of an electrical pulse.

resistance The opposition to the flow of electrical charges. This term is typically applied to circumstances in which a constant voltage is applied to a conductor, such as in DC voltage sources. Resistance varies if there is not a constant voltage, such as in AC voltage sources. In these circumstances, the opposition to the flow of electrical charges is termed impedance.

stimulation parameter The specific combination of parameters such as current/voltage, pulse width, or stimulation frequency (rate). This does not include the electrode configuration of active contacts (anodes and cathodes) in the DBS lead and IPG case.

therapeutic impedance The resistance to electrical flow for those stimulation parameters and electrode configurations that are currently in use to treat the patient. Therapeutic impedance is particularly relevant to safe DBS.

voltage A measure of the electromotive force that moves electrical charges through a conductor.

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